Post-discharge nutritional support in malnourished ill elderly patients

Effectiveness and cost-effectiveness

Floor Neelemaat

Post-discharge nutritional support in malnourished ill elderly patients – effectiveness and cost-effectiveness

Thesis, VU University Medical Center, Amsterdam, The Netherlands
With summary in English and Dutch

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General introduction and outline of the thesis

General introduction

Our population is aging, and the number of Europeans aged between 65-79 years is expected to increase approximately 35% between 2010 and 2030(1). With the probability, the number of malnourished elderly people will increase proportionally.

Aging comes with an increase in health challenges. As elderly people are vulnerable to malnutrition, they often have several co-morbidities that are chronic and progressive. However, malnutrition is not always caused by a disease, it also leads to vulnerability to illness.

According to the literature, malnutrition is estimated to occur in 25-61% of all elderly patients suffering from various diseases(2;3).

We expect that a post-discharge nutritional intervention in malnourished elderly patients will be beneficial for their health and may result in lower health care costs. Figure 1 presents a simplified overview of relations depicted in this thesis.

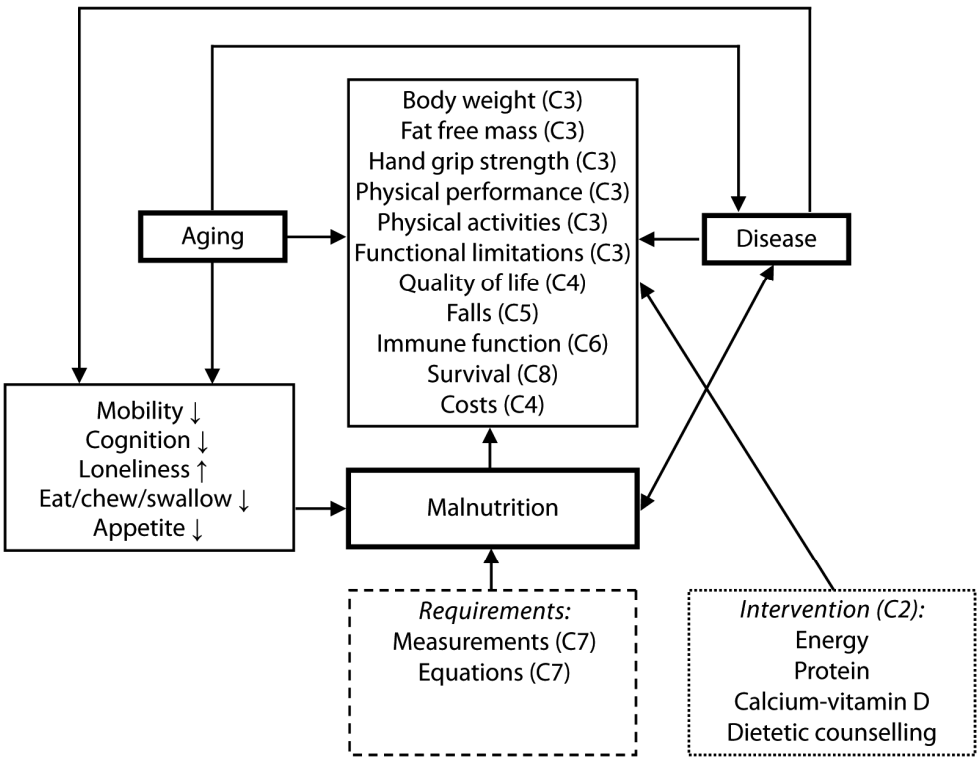

Figure 1: Simplified overview of possible relations between malnutrition, aging and disease and the influence of nutritional interventions on outcomes (C = Chapter number)

Causes of malnutrition

The World Health Organization (WHO) defines malnutrition as "the cellular imbalance between supply of nutrients and energy and the body's demand for them to ensure growth, maintenance, and specific functions".

Previous studies have identified several determinants for malnutrition in elderly individuals, such as disease(4-8), older age(5;9), depression(9-11), cognitive impairment(10), impaired physical functioning(4;10;12;13), dementia(12), toughness in biting and chewing(10;12), vision problems(7), poor appetite(7;10) and stress(7). Some of these causes of malnutrition are irreversible. However, others, e.g. physical functioning, could be improved by accurate nutritional interventions.

Malnutrition also increases ones vulnerability to illness due to the combination of disease and malnutrition. The metabolism weakens and give rise to a vicious circle of infection and undernourishment.

Consequences of malnutrition in elderly

Disease-related malnutrition is associated with adverse effects on clinical outcomes, as has been shown in a large number of studies. These in-hospital adverse effects vary, from impaired wound healing and postoperative complications, to mortality(14). Poor nutritional status has not only been associated with in-hospital adverse effects, but also with adverse effects both pre-admission and post-discharge. As a result of these effects it appears that there is an increased need for re-hospitalization, a higher general practitioner consultation rate, higher medication prescription rate, longer rehabilitation, an increased need for nursing home admission, increased likelihood of requiring home health care following discharge, early institutionalization and significantly higher total mortality (15;16).

Post-discharge nutritional intervention

Due to the short hospitalization period followed by rehabilitation at home, it is not very likely that patients' nutritional status would improve sufficiently during this short period of hospital stay. Therefore, the presence of disease-related malnutrition is increasingly shifting to the post-discharge setting. However, no systematic post-discharge nutritional support is organized in primary health care in The Netherlands.

Treatment of malnutrition in elderly

To date, randomized controlled trials have shown that additional oral nutritional supplements can be effective in improving nutritional status in malnourished elderly people, both in the clinical setting and in the community(17;18). In malnourished hospitalized patients, oral nutritional supplements has demonstrated improved body

weight and attenuated weight loss, to shorten hospital stay and to improve functional status(19). In the community, oral nutritional supplements has been shown to increase activities of daily living, reduce the number of falls and reduce health care utilization(16;20-22).
Oral nutritional supplements has proven to be effective in increasing body weight(22). However, there is limited evidence of effectiveness of post-discharge oral nutritional supplements in malnourished elderly on functional outcomes, like physical performance, physical activities and functional limitations.

Fall incidents
Fall incidents are a common and serious cause of morbidity and mortality in elderly people. Fractures resulting from fall incidents, lead to significant healthcare costs(23). Each year, one in three community-dwelling persons aged 65 years or older, experiences at least one fall incident(24-26). Loss of muscle mass and strength are regarded as important risk factors for falls, functional decline and disability(27).
Malnutrition can decrease muscle mass(28) and both vitamin D deficiency and malnutrition can decrease muscle strength(28;29). In well-nourished community living elderly people at risk of vitamin D deficiency, vitamin D supplementation has shown to improve muscle strength, function, and body balance in a dose-related pattern(30). These benefits include a reduction of fall incidents as shown in epidemiological studies and randomized clinical trials. Several meta-analyses in healthy people support the beneficial effects of vitamin D supplementation on falls (31;32).
Malnutrition is also associated with an increased incidence of falls(33;34), however, studies are insufficient in demonstrating the effects of nutritional intervention in the prevention of fall incidents.

Immune markers
Both malnutrition and advanced age are known to negatively impact the immune system. Malnutrition per se affects nearly all aspects of the immune defence system, but especially impairs cell mediated immunity and resistance to infection(35).
In the elderly, many alterations of both innate and acquired immunity have been described.
Although the emphasis of most research on immunosenescence has been on T cells, there is an increasing realization that the subtle changes seen in parameters of innate immunity, including the acquisition of some characteristics of innate immunity by T cells themselves(39-41), may have more influence on immunity than so far assumed.
Adequate nutrition is believed to play a role in the maintenance and restoration of impaired immune-competence, even in old age(42;43). Not only an adequate intake of

energy and protein play an important role. Also, the correction of certain nutritional deficiencies has been demonstrated to improve the host's immunity, which warrants a place for these nutrients in an adequate diet. However, the optimal intake for a variety of micronutrients, to improve host's immunity, has not been established.
To obtain an idea of the possible changes in the immune system in the period recovering from disease and malnutrition, a broad range of (surrogate) immune markers (interleukins, complement, C-reactive protein, albumin, TNF-α), endocrine markers (growth factors), and micronutrients (iron, ferritin, vitamins) will be assessed, to explore if these different compartments may explain the enhanced recovery of a malnourished ill elderly population following nutritional intervention.

Costs
Health care policy makers need to make informed decisions about whether to fund new health care interventions above or in addition to existing ones. To do this they need information on both the costs and the effects of the alternative treatments, which is provided by cost-effectiveness studies. In a cost-effectiveness study, the costs and consequences of two or more different health care interventions are compared(44).
Studies on cost-effectiveness of nutritional interventions in clinical settings are minimal. In a retrospective cost-analysis of nine randomized controlled trials on nutritional support, the cost savings aggregated between € 500 and € 12000 per patient in surgical, orthopaedic, elderly and stroke patients(17). Cost-effectiveness studies of oral nutritional supplements in the community are lacking.

Energy requirements
Malnutrition is often reversible and can be treated by a dietitian, general practitioner or medical specialist. To establish optimal goals for dietary intake, it is important to predict resting energy expenditure. This requires knowledge of individual energy requirements and relies on accurate methods of assessment. Energy expenditure can be measured by indirect calorimetry and provides an indication of patients' energy requirements(45). This method is not very feasible in most clinical settings, due to time consuming measurements, lack of trained personnel and expensive equipment. In clinical practice, predictive equations to determine resting energy expenditure in malnourished, ill and elderly patients are used as an alternative.
Resting energy expenditure predictive equations have generally been developed in healthy populations or in critically ill patients. Specific equations for predicting resting energy expenditure in malnourished hospitalized elderly patients are lacking.

Cognitive impairment
Malnutrition is associated with dementia and often even a precursor in dementia(46-48). Oral nutritional intake is often inadequate due to impaired ability to complete motor and perceptual tasks, required for eating and drinking and often prevent the older adult from accepting help with feeding from caregivers(49;50).
Mortality rates in patients with dementia (≥ 60 years of age) are more than three times higher in the first year after diagnosis compared to those without dementia(50;51).
Elderly patients, who are not terminally ill and not cognitively impaired, suffering from malnutrition may benefit from standard nutritional therapy if the life expectancy would exceed three months(22;52). Keeping in mind the increased mortality rates of cognitively impaired patients, the question whether or not to start intensive nutritional therapy for a longer period of time in these patients remains yet to be answered.

Outline of the thesis

Only a limited number of studies have been published on the effects of post-discharge nutritional support in malnourished elderly individuals and the results were found to be less impressive or even absent compared to studies on hospitalized patients. Besides, randomized controlled trials in this setting are scarce. In view of these considerations, studies on post-discharge nutritional support in malnourished elderly individuals are imperative. Therefore, this thesis discusses the effectiveness and cost-effectiveness of post-discharge nutritional support in malnourished elderly patients, starting at hospital admission up until three months following discharge.

In **Chapter 2** the design of this randomized controlled trial is described.
In **Chapter 3** the effect of post-discharge nutritional support on the primary outcome, changes in activities of daily living, are evaluated. Secondary outcomes are changes in body weight, body composition, and muscle strength.
In **Chapter 4** the cost-effectiveness of post-discharge nutritional support in malnourished elderly patients, from hospital admission up until three months following discharge, on quality adjusted life years, physical activities and functional limitations is reported.
In **Chapter 5** the effect of the nutritional intervention on falls is presented.
In **Chapter 6** the effect of nutritional intervention on immune markers, endocrine markers and micronutrients is described.
In **Chapter 7** resting energy expenditure predictive equations are compared with measured values at hospital admission and again three months following discharge.

In **Chapter 8** the three-months and one-year survival of malnourished, cognitively impaired (dementia, delirium or a combination of both), hospitalized elderly patients is reported. In addition, potential prognostic characteristics predicting life-expectancy were studied.
In **Chapter 9** the main findings of our studies are summarized, methodological considerations are portrayed and implications for health care are given.

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CHAPTER 2

Study design: effectiveness and cost-effectiveness of post-discharge nutritional support in malnourished elderly patients in comparison with usual care

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Abstract

Background

Malnutrition is a common consequence of disease in elderly patients. Both in hospital setting and in community setting oral nutritional supplements have proven to be effective. However, cost-effectiveness studies are scarce. Therefore, the aim of the present study is to investigate the effectiveness and cost-effectiveness of post-discharge nutritional support in malnourished elderly patients, starting at hospital admission up until three months following discharge.

Methods

The present study is a randomized controlled trial. Patients are included at hospital admission and up until three months following discharge. Patients are eligible to be included when they are ≥ 60 years old and malnourished according to the following objective standards: Body Mass Index (BMI in kg/m^2) < 20 and/or ≥ 5% unintentional weight loss in the previous month and/or ≥ 10% unintentional weight loss in the previous six months. Usual nutritional care will be compared to post-discharge nutritional support (energy and protein enriched diet, two additional servings of an oral nutritional supplement, vitamin D and calcium supplementation, and consultations by a dietitian). Each study arm will consist of 100 patients. The primary outcome parameters will be changes in activities of daily living (determined as functional limitations and physical activity) between intervention and control group. Secondary outcomes will be changes in body weight, body composition, quality of life, and muscle strength. An economic evaluation from a societal perspective will be conducted alongside the randomised trial to evaluate the cost-effectiveness of the intervention in comparison with usual care.

Conclusion

In this randomized controlled trial the effect of post-discharge nutritional support in malnourished elderly patients following hospital discharge will be evaluated and compared to usual care. Primary endpoints of the study are changes in activities of daily living, body weight, body composition, quality of life, and muscle strength. An economic evaluation will be performed to evaluate the cost-effectiveness of the intervention in comparison with usual care.

Background

The primary cause of malnutrition in developed countries is disease. Malnutrition is estimated to occur in 25- 61% of all elderly patients suffering from a variety of diseases(1;2). Unintentional weight loss of ≥ 5% in the previous month and/or unintentional weight loss of ≥ 10% in the previous six months and/or a BMI <20 kg/m^2 are often used as parameters to identify malnutrition.

Disease related malnutrition is associated with adverse effects on clinical outcome, as has been shown in a large number of studies. These adverse effects vary from impaired wound healing and postoperative complications to mortality(3). Poor nutritional status has not only been associated with in-hospital adverse effects, but also with adverse effects both pre-admission and post-discharge. These effects include a trend for increased need for re-hospitalization, significantly higher total mortality, a higher general practitioner consultation rate, higher medication prescription rate, longer rehabilitation, an increased need for nursing home admission, increased likelihood of requiring home health care following discharge and early institutionalization(4;5).

So far, randomized clinical trials have shown that additional oral nutritional supplements (ONS) can be effective in malnourished elderly people, both in the clinical setting and in the community(6). In hospitalized patients ONS has been shown to reduce weight loss, to shorten hospital stay and to improve functional status in malnourished hospitalized patients. In the community ONS has been shown to increase activities of daily living, to reduce the number of falls and to reduce health care utilization(5;7-10).

Furthermore, a meta-analysis, including 31 studies and almost 2500 patients, showed that protein and energy supplementation led to small changes in weight and, more importantly to reduced mortality (RR 0.67; CI 0.52 to -0.87). Also, length of hospital stay was reduced by on average 3.3 days (CI -9.64 to 3.05)(7).

Because nowadays patients spend only a minority of time in hospital and recover at home, it is not very likely that patients' nutritional status will improve during the short period of admission. Therefore, the problem of disease related malnutrition is more and more becoming a post-discharge problem.

For in-hospital patients, studies on cost-effectiveness of nutritional interventions are scarce. In a retrospective cost-analysis of nine randomized controlled trials on nutritional support, the cost savings aggregated between € 503 and € 11696 per patient in surgical, orthopaedic, elderly and stroke patients(6). A recent observational cohort study showed a cost reduction in patients supplied with ONS of € 723 per patient(8). In a prospective study, a reduction of length of hospital stay with one day was achieved with an investment of € 34 per malnourished patient(11).

Cost-effectiveness studies of ONS in the community are lacking and are eagerly awaited for. A nutritional intervention in the post-discharge setting is expected to be

accompanied by higher health care costs than usual care, but these higher costs are negligible compared with the cost-savings they can potentially generate.
The aim of this study is to investigate the cost-effectiveness of post-discharge nutritional support in malnourished elderly patients following hospital discharge as compared to usual care on changes in activities of daily living. Secondary outcomes include changes in body weight, body composition, quality of life, and muscle strength between intervention and control group.

Methods

Design

This study is designed as a randomized controlled trial comparing post-discharge nutritional support with usual nutritional care. The study design is in accordance with the Declaration of Helsinki and has been approved by the Medical Ethics Committee (METC) of VU University Medical Center.
Patients are eligible for this study when they are ≥ 60 years old and malnourished according to the following objective standards: Body Mass Index (BMI in kg/m^2) < 20 and/or, ≥ 5% unintentional weight loss in the previous month and/or ≥ 10% unintentional weight loss in the previous six months. Usual nutritional care will be compared to post-discharge nutritional support (energy and protein enriched diet, two additional servings of an oral nutritional supplement, vitamin D and calcium supplementation, and consultations by a dietitian). The primary outcome parameters will be changes in activities of daily living (functional limitations and physical activity) between the intervention and control group. Secondary outcomes will be changes in body weight, body composition, quality of life, and muscle strength. An economic evaluation from a societal perspective will be conducted alongside the randomised trial to evaluate the cost-effectiveness of the intervention versus usual care.

Feasibility of recruitment and sample size

Earlier studies have shown that 30% of the elderly hospital population is malnourished at admission(12-16). For a clinically relevant difference of 20% in nutritional and functional status with a statistical significance level of 0.05 and a power of 80%, two groups of 80 patients were calculated to be sufficient.
A pilot study showed that inclusion of 140 malnourished patients per year is feasible. Taking into account an expected refusal rate of 30% at inclusion and loss to follow-up of 10% during the three months following discharge, we aim to include two groups of 100, to be reached in approximately two years.

Randomisation
A computerized random number generator will be used to assign patients either to the intervention group or the control group. Patients will be randomized in blocks of ten. At the end of the baseline interview and measurements, the primary investigator opens a consecutively numbered opaque envelope containing the patients' group assignment. Participants, research assistant and researcher are no longer blinded for the intervention from this point. Prior to starting the analyses the researcher (F.N.) will be re-blinded for patients' group assignment.

Population, inclusion and exclusion criteria
All elderly patients (≥ 60 years of age, expected length of hospital admission > 2 days) newly admitted to the wards of internal medicine, traumatology and vascular surgery of the VU University Medical Center will be screened at admission by a dietitian and/or research assistants of nutritional status. These departments represent the (sub)specialties general internal medicine, rheumatology, gastroenterology, dermatology, nephrology, orthopaedics, traumatology and vascular surgery.
Patients will be excluded from the study when they suffer from senile dementia, can not understand the Dutch language or are unable to or willing to give informed consent.

Nutritional status
Patients are being eligible for this study if they are identified malnourished according to the following criteria:

- Body Mass Index (BMI in kg/m^2) < 20 and/or
- ≥ 5% unintentional weight loss in the previous month and/or
- ≥ 10% unintentional weight loss in the previous six months.

Weight (in kg to the nearest decimal) will be measured (with patients wearing light indoor clothes and no shoes) on a calibrated chair scale (Prior MD-1512), with an accuracy of 0.1 kilogram, at admission and three months following discharge. A correction factor for clothes will be made by deducting weight with 2.0 kilograms for men and 1.3 kilograms for women(17).
BMI is calculated as actual weight in kilograms divided by the square of height in meters. As measurement of height is often not feasible in this ill, frail, elderly population, data on height will be retrieved from self-reported height, with an accuracy of 1.0 centimeter. These data will be validated against height derived from knee height measurements (Seca207, Hamburg, Germany; in cm to the nearest decimal) in approximately 800 elderly patients from the same departments at our institute.

Intervention
Control patients will receive 'usual' nutritional care, i.e. hospital intervention only on referral by the treating physician and without standardized post-discharge nutritional support.
Patients assigned to the intervention group strategy will receive standardized post-discharge nutritional support (Appendix 1) starting in hospital and to be continued up until three months following discharge.

Procedure
After obtaining patients' informed consent an inventory will be made of nutritional status, nutritional risk profile and possible confounders. This includes the following baseline characteristics:
- socio-demographic data (age, gender, education level, partner status)
- medical history and medical diagnosis
- anthropometry (weight, height, BMI, percentage involuntary weight loss)
- biochemical parameters (CRP, IGF-1, 25(OH)D)
- mental state (MMSE)(18)
- expected care complexity (COMPRI)(19)

Information on disease, disease severity, disease course, treatment and complications will be retrieved from medical records.
Post-discharge practice will be followed and outcome parameters will be collected for all patients at three months following discharge.

Outcome parameters
Outcome parameters will be measured after inclusion and three months following discharge.
Primary outcome is change in activities of daily living, determined as functional limitations and physical activities. All outcome parameters that will be measured are listed below.

- *Activities of daily living*

Activities of daily living (ADL) will be assessed with a validated questionnaire that measures the degree of difficulties patients experience with six activities: climbing stairs, walking 5 minutes outdoors without resting, getting up and sitting down in a chair, dressing and undressing oneself, using own or public transportation, and cutting one's own toenails(20).

- *Functional limitations*

Functional limitations will be assessed using five difficulty categories, ranging from "No I can not' to 'Yes without difficulty'. Total score will be calculated by summing the scores of all activities, ranging from 0 (does not have any difficulties with the activities) to 6 (has difficulties with all activities).

- *Physical performance*

The performance test of physical function includes time measures of walking speed, rising from a chair, putting on and taking off a cardigan, and maintaining balance in a tandem stand(21-23). To test walking performance a 3 meter walking course is created by a measuring line. Patients are instructed to walk to the other end of the course, to turn 180 degrees, and walk back as quickly as possible. Patients are allowed to use a walking aid if necessary. To test the ability to rise from a chair, patients are asked to fold their arms across their chest and to stand up and sit down five times from a standard hospital chair as quickly as possible. For the cardigan test, patients are asked to put on and take off a cardigan as quickly as possible. To test for balance, patients are asked to stand with one foot placed behind the other in a straight line for at least 10 seconds.
A trained research assistant record the total time needed to complete each test.
Patients who complete the walking test, chair test and cardigan test will be assigned scores between 1 and 4, corresponding to the quartiles of time needed to complete the test, with the fastest time scored as 4. Those who cannot complete the test will be assigned a score of 0. Accordingly the maximum score for these three tests ranges from 0-12 points, after adding up the result of these tree tests.
The balance test will be analyzed separately, yet with the same time classification as described above.

- *Physical activity*

Physical activity will be assessed with the validated LASA Physical Activity Questionnaire (LAPAQ)(24). This face-to-face questionnaire covers the frequency and duration of walking outside, cycling, gardening, sports and household activities during the previous two weeks.
Walking and bicycling for transportation purposes are considered as common daily activities in The Netherlands, and not as sports activities. For the analyses, the total time spent on physical activity of the last two weeks is used (in minutes per day).

- *Quality of life*

Quality of Life will be measured by the SF-12 and Euro-Qol (EQ-5D and EQ-VAS).
The SF-12 contains 12 questions from the SF-36(25). These questions concern functional status -both physical and social functioning-mental health, pain, vitality and evaluation of persons' state of health. With these dimensions two total scores can be calculated; one physical component score and one mental component score(26).
EuroQol (EQ-5D) is a standardised instrument to monitor health outcome(27). This instrument contains five short questions on mobility, self-care, daily activities, pain/discomfort and anxiety/depression with three possible response categories (no problems, moderate problems, severe problems). The EQ-5D scores were used to calculate utilities using the Dutch tariff(28). QALYs were calculated by multiplying the utilities with the amount of time a patient spent in a particular health state. Transitions between health states were linearly interpolated.
Additionally we will administer the EQ-VAS. The EQ-VAS, a visual analogue scale, generates a self-rating of health-related quality of life. The patient rates his/her health state by drawing a line from the box marked "Your health state today" to the appropriate point on the EQ-VAS on a scale of 0 to 100.

- *Hand grip strength*

Hand grip strength (in kg) will be measured using a hydraulic hand dynamometer (Baseline, Fabrication Enterprises Inc., Elmsford, NY, USA). Respondents are asked to perform two maximum force trials with their non-dominant hand. The highest value will be used.
Measured data will be compared to reference values by Mathiowetz. Data will be expressed as percentage of reference value(29).

- *Fall incidents*

Patients will be asked to report all fall incidents weekly in a fall diary for a period of three months following discharge. A fall is defined as "an unintentional change in position resulting in coming to rest at a lower level or on the ground"(30).

- *Bio-electrical impedance spectroscopy*

Bio-electrical impedance spectroscopy (BIS) will be applied to calculate (changes in) body composition. Measurements will be performed at the non-dominant side of the patient, using a Hydra ECF/ICF Bio Impedance Spectrum Analyzer, model 4200 (Xitron Technologies, San Diego, CA, USA). Shoes, socks and jewellery will be removed and patients will be in supine position. Two current electrodes (tetra-polar electrodes (3M red Dot AG/AgCl)) will be placed at the dorsal surfaces of the hand and foot on the distal

position of the second metacarpal and metatarsal, respectively. Two detector electrodes will be placed at the posterior wrist between the styloid processes of the radius and ulna and at the ankle between the tibial and fibular malleoli. With this technique, two body compartments, fat mass (FM) and fat free mass (FFM), can be determined. Patients with a pacemaker will be excluded from this measurement.

- *Resting energy expenditure*

Resting energy expenditure (REE) will be calculated from measurements of oxygen consumption (VO_2) and carbon dioxide production (VCO_2) by with a ventilated hood system, in supine position for 30 minutes, with a metabolic monitor (Vmax Encore n29, Viasys Healthcare, Houten, The Netherlands). Prior to each measurement, gas analyzers will be calibrated with two reference gas mixtures (a. 16% O_2, 4% CO_2, bal. N_2 and b. 26% O_2, bal. N_2 (Viasys)). Patients will be monitored during the measurement to prevent movements or sleeping under the hood.
REE will be calculated from oxygen consumption and carbon dioxide production by using the equation of Weir(31).

- *Dietary intake*

Dietary intake will be obtained by asking in broad outlines for patients' mean daily intake of food and drinks in the two weeks prior to admission to the hospital and three months following discharge.

- *Biochemical parameters CRP, IGF-1, 25(OH)D*

Two blood samples per patient will be obtained: the first on the day of inclusion and the second three months following discharge. We will measure CRP, IGF-1 and 25 (OH)D in both samples. The blood samples will be centrifuged and stored at -80°C. All blood samples will be analyzed simultaneously after completing full data collection.
C-reactive protein (CRP in mg/l) is a member of the class of acute-phase reactants as its levels rise dramatically during inflammation processes. Plasma concentrations of C-Reactive Protein (CRP) will be measured with an automated latex-enhanced immunoturbidimetric assay on a Modular P800 analyzer (Roche Diagnostics, Almere, The Netherlands).
Insulin-like growth factor (IGF-1 in µg/l) will be obtained to observe over or under production of growth-hormone. Serum levels of IGF-1 will be measured with a Immulite 2500 analyzer (Siemens, Deerfield, IL, USA).
Serum 25(OH)D (in nmol/l) will be obtained to observe differences in vitamin D levels following three months supplementation of vitamin D in the intervention group. This

will be determined using a competitive protein binding assay (Nichols Diagnostics, San Juan Capistrano, CA, USA).
All analyses will be performed at department of Endocrine Laboratory of the VU University Medical Center.

- *Costs*

Costs will be measured from a societal perspective. Direct health care costs include the costs of post-discharge nutritional support (nutritional supplements plus dietitian), hospitalization, additional visits to other health care providers (general practitioner, medical specialist), prescription and over-the-counter medication, professional home care. Direct non-health care costs of paid and unpaid help and indirect cost of absenteeism of paid and unpaid work will also be included.
Data on the use of nutritional support will be registered by the dietician implementing the post-discharge nutritional intervention. Data on health care utilization during hospitalization will be retrieved from medical records and the hospital information system. Use of other health care resources following discharge will be collected through two identical cost diaries each spanning a period of 6 weeks. Medication data will be obtained from the patients' pharmacies.
Health care utilization will be valued using standard costs from the Dutch guidelines for cost analysis in health care research(32). If there are no standard costs available, tariffs or prices from health care providers themselves or professional organizations will be used. The costs of medication will be estimated on the basis of prices charged by the Royal Dutch Society for Pharmacy.

Economic evaluation
The aim of the economic evaluation will be to determine and compare the total costs for patients receiving either post-discharge nutritional support or usual care, and to relate these costs to the effects of the interventions.
Incremental cost-effectiveness ratios (ICERs) will be calculated by dividing the difference in mean total costs between the two interventions by the difference in mean effects between the two interventions. The ICERs will be calculated for the primary clinical effect measures of the trial, i.e. functional status and ADL. Cost-utility ratios will also be calculated.
Bootstrapping will be used for pair-wise comparison of the mean differences in total costs between the intervention groups. Confidence intervals will be obtained by bias corrected and accelerated (Bca) bootstrapping using 5000 replications(33). To estimate the uncertainty surrounding the ICERs bias corrected accelerated bootstrapping (5000

replications) will be used. The bootstrapped cost-effect pairs will be plotted on cost-effectiveness planes and will be used to estimate cost-effectiveness acceptability curves.

Organization
The primary investigator is responsible for the informed consent procedure, final patient selection, measurements, analysis and reports. The primary investigator will be assisted by a research assistant.
Data flow will be controlled by the primary investigator, using an administrative database system. Data-entry and control will be conducted by a research assistant under supervision of the investigator. The primary investigator is responsible for the data cleaning and analysis.

Statistical analyses
All analyses will be performed according to the intention-to-treat principle. 95% confidence intervals will be calculated for the differences in percentages and means. Logistic regression will be used to analyze dichotomous variables, Poisson regression for the count-variables and linear regression for continuous variables. Ceiling and floor effects will be taken into account in the analysis of the questionnaires.
In order to test the independent contribution of the intervention on the outcome variables, multivariate regression analysis will be used to adjust for the possible confounders.

Discussion

When designing the study protocol we had to make a number of considerations, which may lead to the following strengths and weaknesses:
Firstly, we have chosen a strict definition of malnutrition, because the most malnourished group is most likely to benefit from oral nutritional support. Since we have used the described cut-off points for malnutrition in previous studies as well, we expect that it is feasible to include a sufficient number of patients in the proposed study.
Secondly, we have chosen not to use strict exclusion criteria, but to include all eligible patients, even though they are suffering from a variety of (chronic) diseases. Their homogeneity stems from their age (≥ 60 years of age), degree of malnutrition (severe malnutrition) and background of disease (mainly non-surgical). We have performed earlier studies with this same group of relatively unselected patients with positive results of the nutritional intervention (after correcting for possible confounders such as age, sex, ethnicity, care complexity, disease etc) in comparison with usual care(11;34). Moreover, if the results of a broad study like this one are positive, it justifies wide implementation,

because the included group is representative for a mixed elderly hospital population; in contrast, selection of a more specific group would make the intervention less applicable to other patients groups. Thirdly, for research purposes, standardized oral nutritional supplementation is chosen because simply advising patients to increase their intake by eating more has not proven to be a solution that can be relied on. From earlier studies, it is known that providing extra supplements does increase energy intake and leads to weight gain, in contrast to dietary advice alone (without extra supplements)(10;35;36).
Fourthly, the follow-up period of three months is chosen because this seems a reasonable recovery period following discharge in this particular patient group. Also, it is known that adherence of patients to take extra supplements diminishes after three months(37;38). By making regular phone calls to the patients we try to maintain adherence.
Fifthly, care should be taken of in-hospital contamination between treatment groups. The majority of in-hospital patients will not be supplemented additional nutrition, either because they are not malnourished (± 70%) or because they are randomized to the control strategy (50% of the study population, 15% of the total population). Except for the primary investigator and research assistant, doctors and nurses will not be aware of the reason for not-supplementing. Thus we expect to be able to prevent contamination between treatment groups. In addition, hospital admission will last only 10 to 15 days and post-discharge treatment will be approximately three months. We expect that the post-discharge period to account for the majority of the effects. Contamination between treatment groups in not likely to occur following discharge.
Finally, this is the first prospective, randomized controlled trial evaluating whether post-discharge nutritional support is effective and cost-effectiveness when compared to usual care.

Conclusion

In this study we will evaluate in a randomized controlled trial whether post-discharge nutritional support, compared to usual care, is effective and cost-effective, in malnourished elderly patients. We will determine changes in activities of daily living, physical activity, functional limitations, body weight, body composition, quality of life, and muscle strength between the intervention and control group during the period between hospitalization up until three months following discharge.

Appendix 1

Patients allocated to the intervention group received standardized nutritional support starting in hospital and continuing until three months following discharge:

- Energy and protein enriched diet (during the in-hospital period)
- Two additional servings of an oral nutritional supplement (Nutridrink®, Nutricia N.V., Zoetermeer, The Netherlands), leading to an expected increase in intake of 2520 kJ/d and 24 g protein/d (during the entire study period)
- 400 IU vitamin D3 and 500 mg calcium (Calci-Chew D3®, Nycomed bv, Hoofddorp, The Netherlands) per day (during the entire study period)
- Telephone counselling by a dietitian to give advice and to stimulate adherence to the proposed nutritional intake (every second week following discharge from the hospital, 6 in total)

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CHAPTER 3

Post-discharge nutritional support in malnourished elderly patients decreases functional limitations

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Abstract

Background

Older people are vulnerable to malnutrition, which leads to negative outcomes. This study evaluates the effectiveness of nutritional supplementation in malnourished elderly patients following hospital discharge.

Methods

Hospital-admitted malnourished elderly patients (≥ 60 years of age) were randomized to receive either nutritional supplementation (energy and protein enriched diet, oral nutritional supplements, calcium-vitamin D supplement, telephone counselling by a dietitian) for 3 months post-discharge or usual care. Outcomes were functional limitations, physical performance, physical activities, body weight, fat free mass, and handgrip strength. Measurements were performed at hospital admission (baseline) and at 3 months following discharge. Data were analyzed according to the intention-to-treat principle.

Results

A total of 210 patients were included, 105 in each group. Body weight increased more in the intervention group than in the control group; this was statistically significant for the highest body weight category (mean difference 3.4 kg, 95% CI 0.2 to 6.6). Functional limitations decreased more (mean difference -0.5 (95% CI -1.0 to 0.1) in the intervention group than in the control group. When excluding patients who had already received nutritional support prior to the start of the study, this reached significance. No statistically significant differences could be demonstrated for physical performance, physical activities, fat-free mass, or handgrip strength.

Conclusion

Three months of oral nutritional support to malnourished elderly decreased functional limitations and increased body weight. It can be questioned if a follow-up of only 3 months was not too short to detect differences on physical performance and physical activities as well.

Background

Disease-related malnutrition is associated with adverse effects on clinical outcomes, such as a higher frequency of general practitioner consultations, an increased need for re-hospitalization, and significantly higher mortality(1-3).

Currently, patients spend only a minimum amount of time in hospital and recover at home. Therefore, it is not very likely that the nutritional status of patients will improve during the short period of hospitalization. Thus, the problem of disease-related malnutrition is increasingly becoming a post-discharge problem.

Especially elderly people are vulnerable to malnutrition, as they often suffer from several chronic or progressive co-morbidities. Recently, Milne et al.(4) published a meta-analysis on the effects of protein and energy supplementation in malnourished elderly. For hospitalized patients they found positive effects of oral nutritional supplements (ONS) on complications, mortality rates, and on weight changes. For other relevant outcomes though, indicating improvement in quality of life, such as grip strength, activities of daily living, physical performance, and functional limitations, no effects were found. Only a limited number of studies have been published on post-discharge nutritional support in malnourished elderly individuals and results were found to be less prominent or even absent. Besides, randomized controlled trials in this setting are scarce. In view of these considerations, studies on post-discharge nutritional support in malnourished elderly individuals are imperative. Therefore, we designed a randomized controlled trial to investigate the effects of post-discharge nutritional support in malnourished elderly individuals, especially with respect to short-term clinically relevant health outcomes, from hospital admission until 3 months following discharge. The primary outcome parameters were changes in activities of daily living (functional limitations and physical activity) between the intervention and control groups. Secondary outcomes were changes in body weight, body composition, and muscle strength.

Methods

Design

The study was designed as a randomized controlled trial comparing post-discharge nutritional support with usual nutritional care in malnourished elderly patients, with a follow-up of 3 months following discharge.

The study design is in accordance with the Declaration of Helsinki and has been approved by the Medical Ethics Committee of VU University Medical Center. Details about the design were more extensively described elsewhere(5).

Randomization

A computerized random number generator was used to assign patients, in blocks of 10, to either the intervention group or the control group. At the end of the baseline interview and measurements, the primary investigator (F.N.) opened a consecutively numbered opaque envelope containing the patients' group assignment. Participants, research assistant, and researcher were no longer blinded for the intervention from this point. When performing the analyses, the primary investigator was not aware of the patients' group assignment.

Patients

A dietitian or research assistant screened the nutritional status in all elderly patients (inclusion criteria: ≥ 60 years of age, expected length of hospital admission > 2 days) newly admitted to the departments of general internal medicine, rheumatology, gastroenterology, dermatology, nephrology, orthopaedics, traumatology, and vascular surgery of the VU University Medical Center, Amsterdam.

Patients were excluded from the study when they suffered from senile dementia, could not understand the Dutch language, or were unable or willing to give informed consent.

Screening nutritional status

Patients were eligible for this study if they were identified as malnourished according to the following criteria:

- Body Mass Index (BMI in kg/m^2) of 20 or lower and/or
- 5% or more unintentional weight loss in the previous month and/or
- 10% or more unintentional weight loss in the previous six months.

Weight (in kg to the nearest decimal) was measured (with patients wearing light indoor clothes and no shoes) on a calibrated chair scale (Prior MD-1512; Servo Berkel Prior B.V., Katwijk, The Netherlands), with an accuracy of 0.1 kg, at admission and three months following discharge. A correction factor for clothes was made by deducting weight with 2.0 kg for men and 1.3 kg for women(6). As measurement of height was often not feasible in this ill, frail, elderly population, data on height were retrieved from self-reported height, with an accuracy of 1.0 cm. BMI was calculated as actual weight in kilograms divided by the square of height in meters. Unintentional weight loss was calculated based on recalled body weight in the previous month and previous 6 months.

Control group

Patients allocated to the control group received usual care, i.e., they were given nutritional support only on prescription by their treating physician, which means that in general they did not receive post-discharge nutritional support.

Intervention group

Patients allocated to the intervention group received standardized nutritional support starting in hospital and continuing until 3 months following discharge:

- Energy and protein enriched diet (during the in-hospital period)
- Two additional servings of an oral nutritional supplement (Nutridrink®, Nutricia N.V., Zoetermeer, The Netherlands), leading to an expected increase in intake of 2520 kJ/d and 24 g protein/d (during the entire study period)
- 400 IU vitamin D3 and 500 mg calcium (Calci-Chew D3®, Nycomed bv, Hoofddorp, The Netherlands) per day (during the entire study period)
- Telephone counselling by a dietitian to give advice and to stimulate adherence to the proposed nutritional intake (every second week following discharge from the hospital, 6 in total)

Adherence

Adherence with oral nutritional supplements and calcium-vitamin D supplementations was checked by asking patients every other week how many supplements they had taken. This was double-checked with both the pharmaceutical service center, which delivered the oral nutritional supplements at home, and the patient's pharmacy, which delivered the calcium-vitamin D supplements.

Functional limitations, physical activities, and physical performance

Activities of daily living were assessed with two validated questionnaires, the LASA Functional Limitation Questionnaire(7) and the LASA Physical Activity Questionnaire(8;9).

The Functional Limitation Questionnaire measures the degree of difficulties patients experience with six activities, for example, climbing stairs and getting up and sitting down in a chair (score 0–6).

The Physical Activity Questionnaire is a face-to-face questionnaire that measures the frequency and duration of, for example, walking outside, sports, and household activities (score 0–6).

Additionally, physical performance was measured to describe functional capability(10;11). Patients were evaluated by examining walking speed, ability to rise from a chair, to put on and take off a cardigan, and standing balance (score 0–16).

An increase in physical activities and physical performance and a decrease in functional limitations was considered a positive result.

Bio-electrical impedance spectroscopy and handgrip strength

Bio-electrical impedance spectroscopy was applied to determine changes in fat free mass (in kg)(12;13). Measurements were performed using an ECF/ICF Bio Impedance Spectrum Analyzer, Hydra 4200 (Xitron Technologies, San Diego, CA, USA).

Handgrip strength (in kg) was applied to determine changes in maximum peripheral muscle function. Measurements were performed with a hydraulic hand dynamometer (Baseline, Fabrication Enterprises Inc., Elmsford, NY, USA)(14).

Statistical methods

- *Sample size calculation*

Earlier studies have shown that 30% of the elderly hospital population is malnourished at admission. For a clinically relevant difference of 20% in nutritional and a 0.5-point difference in functional status with a statistical significance level of .05 and a power of 80%, two groups of 80 patients were calculated to be sufficient.

- *Statistical analyses*

The statistical analyses for the main analyses were performed according to the intention-to-treat principle. Changes in several key variables, such as body weight and results on questionnaires, could not be calculated in patients without follow-up data, owing to withdrawal or death; therefore, patients with missing data were excluded from the intention-to-treat analysis. An analysis with imputed data was performed as well, conforming to the last-observation carried-forward principle.

To exclude effects of earlier nutritional support, we also performed a per protocol analysis, in which the only patients included were those who had not received nutritional support and/or dietetic counselling prior to the start of the study.

Standard descriptive statistical methods were used to express means, standard deviations, percentages, frequencies, changes in variables, and minimum and maximum values. Differences in nominal variables between the intervention and control were tested by chi-square tests. Differences in interval and ratio variables between the groups were tested by independent t-tests.

Linear regression analyses were performed to control for confounding and effect modification. Because body weight at baseline was found to be an effect modifier, we corrected for body weight at baseline by creating different body weight categories by tertiles. The 95% confidence intervals were based on 2-sided tests. Statistical analyses were performed using the SPSS system for Windows, version 16.0 (SPSS, Chicago, IL, USA).

Results

We screened 3291 elderly patients on nutritional status (Figure 1), 2716 of whom did not meet the malnutrition criteria; 575 patients remained eligible for enrolment in the study, of whom another 365 patients were excluded for reasons described in Figure 1. There were no differences in gender, BMI, unintentional weight loss in the last month, and unintentional weight loss in the past 6 months between the excluded and the included patients. Patients in the excluded group were significantly older: 77.4 (standard deviation [SD] 9.7) versus 74.6 (SD 9.5) years of age (95% confidence interval [CI] 1.1 to 4.4). In total, 210 patients were included in the study: 105 patients in the intervention group and 105 patients in the control group. Mean age was 74.5 (SD 9.5) years (range 60-97 years) and 55.2% of patients were female. At baseline there were no statistically significant differences in patient and clinical characteristics between the intervention and control groups (Table 1).

For 60 patients, the follow-up data were incomplete: in the intervention group, 16 patients withdrew and 14 patients died; in the control group, 19 patients withdrew and 11 patients died. Patients without complete follow-up were older: 77.3 (SD 9.5) versus 73.4 (SD 9.3) years (95% CI 1.0 to 6.7). There were no statistically significant differences in gender, BMI, unintentional weight loss in the last month/last 6 months, home situation, residence pre-admission, consulting dietitian, and use of supplemental drinks. Adherence to oral nutritional supplements, calcium-vitamin D supplementation, and dietetic counselling was high: 80%, 96%, and 96%, respectively.

Changes in functional limitations, physical performance, and physical activities between the intervention and the control groups are presented in Table 2.

There was a positive, however non significant, trend for a reduction in functional limitations for both men and women in the intervention group (mean difference -0.5, 95% CI -1.0 to 0.1). For physical performance and physical activities, no statistically significant improvement could be demonstrated by the intervention strategy.

Changes in body weight, handgrip strength, and fat-free mass between intervention and control groups are presented in Table 3.

Body weight at baseline was found to be an effect modifier, and therefore results are presented in different categories of body weight. Overall, patients in the intervention group tended to gain more weight (mean difference 11.5 kg, 95% CI -0.2 to 3.1) than controls. These effects were statistically significant for the highest body weight category (mean difference 13.4 kg, 95% CI 0.2 to 6.6). For fat-free mass and handgrip strength, no statistically significant differences could be demonstrated by the intervention strategy.

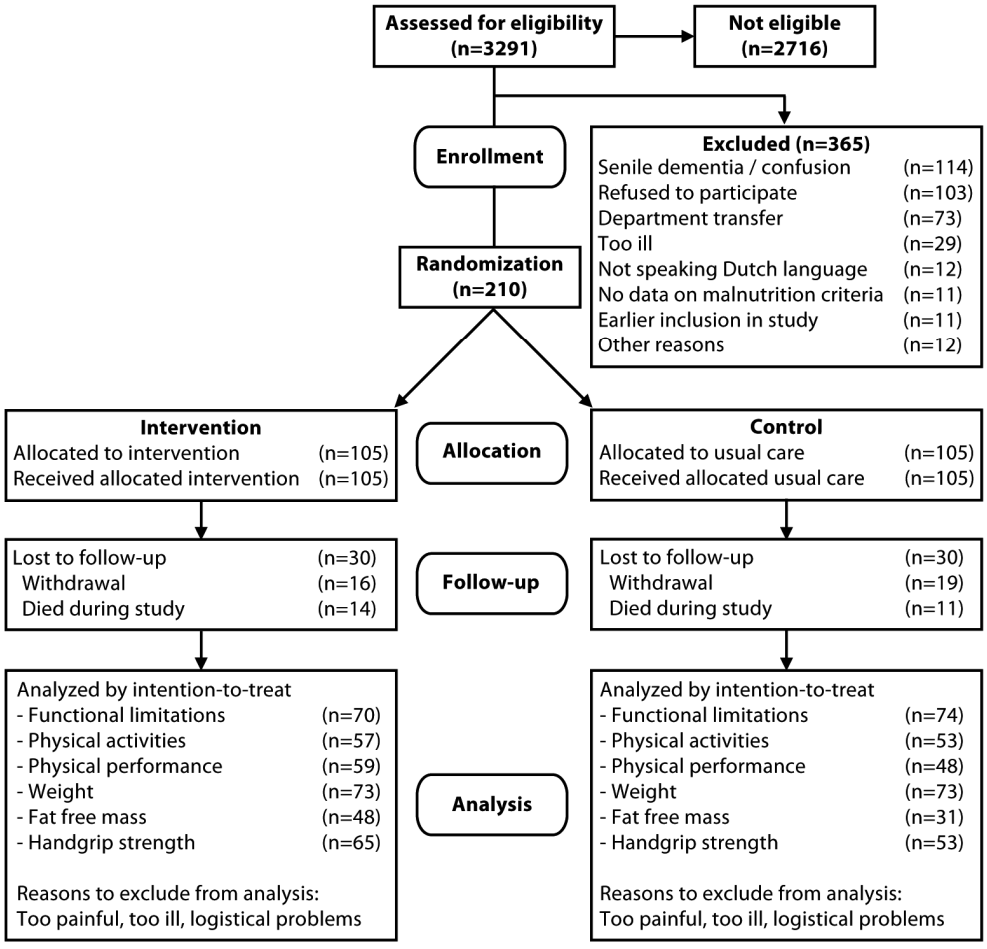

Figure 1: The CONSORT flow chart

Only limited follow-up data on fat free mass were available. Of the 150 patients with complete follow-up data, only 79 fat free mass measurements are presented. Reasons for missing data were as follows: physical impossibility to participate (41 patients), unreliable results on measurement (18 patients), refusal to participate (8 patients), and dysfunction of the equipment (4 patients). We observed more missing data in control patients (missing, n=44) than in intervention patients (missing, n=27). In addition, the most severely ill patients were those showing missing data (positive selection).

Table 1: Baseline and clinical characteristics of included patients

Characteristics	Intervention group (n=105)	Control group (n=105)
Gender – no. females (%)	56 (53.3)	60 (57.1)
Age, y – mean (±SD)	74.6 (9.7)	74.4 (9.3)
Home situation – no. (%)		
Living alone	54 (51.4)	54 (51.4)
Living with partner / family	51 (48.6)	51 (48.6)
Residence pre-admission – no. (%)		
Living independently	86 (81.9)	90 (85.7)
Nursing home	9 (8.6)	11 (10.5)
Home for the elderly	6 (5.7)	4 (3.8)
Hospital	4 (3.8)	0
Consulting dietician pre-admission – no. (%)	25 (23.8)	23 (21.9)
Use of supplemental drinks pre-admission – no. (%)	23 (21.9)	30 (28.6)
Body Mass Index in categories – no. (%)		
BMI ≤ 20	58 (55.2)	56 (53.3)
BMI 20 – 25	32 (30.5)	39 (37.1)
BMI ≥ 25	15 (14.3)	10 (9.6)
Weight change last month – % (range)	-4.5 (-19.8 to 16.9)	-4.0 (-35.7 to 17.7)
Weight change last six months – % (range)	-9.4 (-30.1 to 16.9)	-9.1 (-30.3 to 26.2)
Medical specialty – no. (%)		
Surgical		
Traumatology	7 (6.7)	3 (2.9)
Vascular surgery	13 (12.4)	16 (15.1)
Non surgical		
Internal medicine	32 (30.5)	43 (41.0)
Gastroenterology	30 (28.6)	30 (28.6)
Nephrology	14 (13.3)	8 (7.6)
Rheumatology	5 (4.8)	4 (3.8)
Dermatology	4 (3.7)	1 (1.0)
Primary diagnosis in categories – no. (%)		
Acute infections	20 (19.0)	13 (12.4)
Vascular disease	16 (15.2)	16 (15.2)
Kidney insufficiency	13 (12.4)	8 (7.6)
Fractures, orthopaedic disorders	12 (11.4)	10 (9.5)
Malignant neoplasm	10 (9.5)	18 (17.1)
Chronic bowel disease	10 (9.5)	17 (16.2)
Diabetes Mellitus, heart failure and other	10 (9.5)	10 (9.5)
Bleeding in gastrointestinal tract	7 (6.8)	8 (7.6)
Liver, gall and pancreas insufficiency	7 (6.7)	5 (4.9)

There were no statistically significant differences between intervention group and control group

Table 2: Changes in functional limitations, physical performance and physical activity at three months follow-up in comparison with baseline between intervention and control group

Characteristics	Intervention group Δ	Control group Δ	Difference (95% CI)
Functional limitations score	n=70	n=74	
Total (n=144)	-0.3 (1.2)	0.2 (1.5)	-0.5 (-1.0 to 0.1)
Physical performance score	n=59	n=48	
Total (n=107)	3.0 (4.2)	2.1 (5.4)	0.8 (-1.0 to 2.6)
Physical activity score	n=57	n=53	
Total (n=110)	0.5 (1.5)	0.6 (1.5)	-0.1 (-0.7 to 0.5)

Data are presented as mean (±SD)

Table 3: Changes in body weight, fat-free mass, and handgrip strength at three months follow-up in comparison with baseline between intervention and control group

Characteristics	Intervention group Δ	Control group Δ	Difference (95% CI)
Body weight in kg corrected for baseline body weight tertiles	n=73	n=73	
Total <53.6 kg (n=45)	2.2 (3.4)	3.0 (4.2)	-0.8 (-3.2 to 1.5)
Total 53.6-63.9 kg (n=50)	2.7 (3.8)	0.9 (5.6)	1.8 (-0.9 to 4.4)
Total > 63.9 kg (n=51)	2.5 (4.2)	-0.9 (6.8)	**3.4 (0.2 to 6.6)**
Fat free mass in kg	n=48	n=31	
Total (n=79)	3.3 (4.3)	2.8 (4.1)	0.5 (-1.5 to 2.4)
Handgrip strength in kg	n=65	n=53	
Total (n=118)	0.2 (5.6)	1.0 (6.7)	-0.8 (-3.0 to 1.5)

Data are presented as mean (±SD)

Table 4: Per protocol analysis for changes in functional limitations, physical performance, physical activity, body weight, fat-free mass, and handgrip strength at three months follow-up in comparison with baseline between intervention and control groups

Characteristics	Intervention group Δ	Control group Δ	Difference (95% CI)
Functional limitation score	n=47	n=50	
Total (n=97)	-0.4 (1.4)	0.2 (1.5)	**-0.6 (-1.2 to -0.0)**
Physical performance score	n=39	n=34	
Total (n=73)	2.6 (4.2)	2.6 (5.8)	0.1 (-2.3 to 2.4)
Physical activity score	n=38	n=36	
Total (n=74)	0.7 (1.4)	0.5 (1.7)	0.2 (-0.5 to 0.9)
Body weight in kg	n=49	n=49	
Total (n=98)	2.6 (4.1)	0.4 (5.6)	**2.2 (0.3 to 4.2)**
Fat free mass in kg	n=31	n=19	
Total (n=50)	3.4 (3.5)	3.1 (4.9)	0.3 (-2.1 to 2.7)
Handgrip strength in kg	n=44	n=36	
Total (n=80)	-0.2 (5.3)	1.8 (4.7)	-2.0 (-4.3 to 0.2)

Data are presented as mean (±SD)

Table 4 shows the results of only those patients who had not received nutritional support and/or dietetic counselling prior to the start of the study (the so-called per protocol analysis). Functional limitations were now found to decrease statistically significant more in the intervention group than in the control group. Also, body weight increased statistically significant more in the intervention group. No statistically significant differences between groups could be demonstrated for fat-free mass, handgrip strength, physical performance, and physical activities.
Analysis performed after applying the last-observation carried-forward strategy, to deal with missing data, did not change results (data not presented).

Discussion

This is one of the first randomized controlled trials showing positive effects of a three months nutritional intervention to malnourished elderly on functional limitations and body weight. The nutritional intervention is reliably responsible for these effects, as the effects increased when we excluded patients who where already on nutritional support prior to the trial.
Only very few other studies have reported positive effects on the so-called clinically relevant outcomes. Woo et al.(15) reported a significant decrease in functional limitations following one month of oral nutritional support. According to the randomized controlled trials of Bunout et al. (16) and Kukuljan et al.(17), functional effects could possibly improve more by combining oral nutritional supplements with physical training, which may be a goal for a future nutrition intervention trial.
For activities of daily living, our study did not show significant improvements, which is in line with Milne's review(4) in which none of the reviewed studies had a significant effect on activities of daily living. Only 2 studies reported an improvement, but in subgroups only. In the study by Volkert et al.(18), activities of daily living improved for the most malnourished patients. In the study by Potter et al.(19), activities of daily living improved in the subgroup of patients who best accepted the supplements.
A striking and positive point of this study is the high adherence to the supplements. Adherence to oral nutritional supplements was 80%, which is much higher than in many of the previous studies(1). In contrast to other studies, our patients were counselled by a dietitian every other week, i.e., 6 times during the entire study period. We hypothesize that part of the positive effects can be attributed to this counselling. In the study of McMurdo et al.(20), a trial very similar to ours, adherence to oral nutritional supplements was only 45%, but patients in this trial received no dietetic counselling. They reported significant improvement of handgrip strength in the supplemented group, but no significant differences in activities of daily living.

Despite the complexity and severity of illness in the patient groups, we still were able to complete follow-up on 71% of the patients. Most patients who withdrew did so because of terminal illness. A more detailed patient selection at baseline, identifying patients in whom malnutrition is an indication of end-stage disease, rather than an indication of a deplored nutritional status, could possibly add to the effectiveness of the intervention. We plan to study metabolic, immune, and inflammatory parameters in these patients in the near future, to be able to identify those patients who are likely to benefit most from nutritional support.

One of the strengths of this study is that it was a randomized controlled trial, including malnourished patients only, with properly concealed allocation and intention-to-treat analyses. Also, this study focused on primary outcomes of relevance (i.e., physical activities and functional limitations), rather than on weight changes only.

We presume that the order of effects would be weight gain first, then improvement in physical activities, and finally improvement in quality of life. However, in conformity with earlier studies by other authors, we were unable to show effects on physical activities and quality of life in these ill, frail, elderly patients after only three months of nutritional intervention. We therefore hypothesize that a study with an intervention period of six months would probably have resulted in effects on other relevant end points as well.

At inclusion into the study, 17% of patients were found to be malnourished. This is moderately lower than generally described in reviews(1). This can probably be explained by the tight definition of malnutrition in our study. Other studies in elderly often use BMI cut-off values higher than 20, thus defining more patients as malnourished(21;22). Another patient mix, in diagnosis and prognosis, could also be an explanation for this difference(23). Finally, the patients with a life expectancy of fewer than 3 months, probably the most severely ill and most severely malnourished ones, were excluded.

Unfortunately, not all patients had complete data on all measurements. Questionnaires (for example, the functional limitations questionnaire) were complete for almost all patients, whereas function tests were less complete. The least follow-up data were obtained for the measurement of body composition, with physical impossibility to undergo the measurement being the most important reason. Future studies should take into account the impediments of functional tests in such a frail study population.

In addition, the most severely ill patients showed the most missing data (positive selection). Thus, we hypothesize that more complete data would have pointed toward larger effects in favour of the intervention group.

Conclusion

Ageing comes with decreased disability and decreased quality of life. In geriatric medicine, all interventions aim at limiting further decline. We were positively surprised that a relatively short nutritional intervention to malnourished elderly was effective in decreasing functional limitations and increasing body weight. Therefore, nutritional intervention, consisting of protein, energy, vitamin D, and calcium, may be a promising, cheap, and easy intervention strategy to maintain - or even improve - nutritional status in malnourished elderly. However, we need to interpret our results with caution: our findings were especially observed in patients who had not received nutritional intervention prior to the trial and no significant improvements were observed for physical activities or muscle strength. We presume that a longer intervention period might lead to relevant differences for these parameters as well. In addition, future research on cost-effectiveness and mechanisms of improvement is necessary.

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CHAPTER 4

Oral nutritional support in malnourished elderly decreases functional limitations with no extra costs

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Abstract

Background

Elderly people are vulnerable to malnutrition which leads to increased health care costs. The aim of this study was to evaluate the cost-effectiveness of nutritional supplementation from a societal perspective.

Methods

This randomized controlled trial included hospital admitted malnourished elderly (≥ 60 years) patients. Patients in the intervention group received nutritional supplementation (energy and protein enriched diet, oral nutritional supplements, calcium-vitamin D supplement, telephone counselling by a dietician) until three months following discharge from hospital. Patients in the control group received usual care (control). Primary outcomes were Quality Adjusted Life Years (QALYs), physical activities and functional limitations. Measurements were performed at hospital admission up until three months following discharge. Data were analyzed according to the intention-to-treat principle and multiple imputation was used to impute missing data. Incremental cost-effectiveness ratios were calculated and bootstrapping was applied to evaluate cost-effectiveness. Cost-effectiveness was expressed by cost-effectiveness planes and cost-effectiveness acceptability curves.

Results

210 patients were included, 105 in each group. After three months, no statistically significant differences in quality of life and physical activities were observed between groups. Functional limitations decreased significantly more in the intervention group (mean difference -0.72, 95% CI -1.15 to -0.28). There were no differences in costs between groups. Cost-effectiveness for QALYs and physical activities could not be demonstrated. For functional limitations we found a 0.95 probability that the intervention is cost-effective in comparison with usual care for ceiling ratios > € 6500.

Conclusion

A multi-component nutritional intervention to malnourished elderly patients up until three months following hospital discharge leads to significant improvement in functional limitations and is neutral in costs. A follow-up of three months is probably too short to detect changes in QALYs or physical activities.

Background

Elderly people are vulnerable to malnutrition secondary to chronic or progressive disease(1;2). The number of European aged between 65-79 years is expected to increase with approximately 35% between 2010 and 2030(3). In the Netherlands, people aged 65 years and older are the most rapidly growing age group. In 2009, there were 2,5 million adults in this age group. In 2040 the number of adults of 65 years and older will have grown to 4,5 million(4;5). Thus, also malnutrition is expected to become a larger problem in the near future.

Next to the expected increase in malnutrition prevalence rates in elderly, its treatment will quickly shift from the hospital setting to the community. In our university hospital, for example, the mean hospital admission time for patients ≥ 60 years of age, has decreased from 15 to 9 days between 1999 and 2009.

Disease-related malnutrition is associated with adverse clinical outcomes, as has been shown in a large number of studies. These adverse effects vary from impaired wound healing and postoperative complications to increased mortality(6).

Poor nutritional status has not only been associated with in hospital adverse effects, but also with adverse effects both preadmission and post-discharge. These effects include an increased need for (re-)hospitalization, a higher mortality, a higher frequency of general practitioner consultations, a higher frequency of medication prescriptions, longer rehabilitation, an increased need for nursing home admission, an increased likelihood of requiring home health care following discharge, and earlier institutionalization(7;8).

Thus, malnutrition leads to increased health care costs. Calculations extrapolated from the United Kingdom to the EU situation indicate that as many as 20 million Europeans are at risk for malnutrition and that the cost for society of malnutrition is around 120 billion euros annually, mostly due to the extended stay of malnourished patients in hospital and in long-term care facilities(9;10).

Randomized controlled trials have shown that additional oral nutritional supplements (ONS) can be effective in malnourished elderly people, both in hospitalized patients and in the community(11). In hospitalized patients, ONS has been shown to reduce unintentional weight loss, to shorten hospital stay and to improve functional status in malnourished hospitalized patients(6). In the community, ONS has been shown to increase activities of daily living, to reduce the number of falls and to reduce health care utilization(12-16).

Evidence on the cost-effectiveness of ONS in the community is needed considering the large economic consequences of malnutrition. However, cost-effectiveness studies of ONS in the community are lacking. Therefore, the aim of this study was to investigate the cost-effectiveness of post-discharge nutritional support in malnourished elderly

patients, from hospital admission up until three months following discharge. We hypothesized that the costs of a nutritional intervention will be offset by costs of hospitalizations and other health care utilization.

Methods

Design

The study was designed as a randomized controlled trial comparing nutritional support from hospital admission up until three months following discharge (intervention) with usual nutritional care (control) in malnourished elderly patients.

The study design is in accordance with the Declaration of Helsinki and has been approved by the Medical Ethics Committee (METC) of VU University Medical Center, Amsterdam. The design has been more extensively described elsewhere(17).

Randomization

A computerized random number generator was used to assign patients to either the intervention group or the control group. Block randomization in blocks of ten was used to ensure equal numbers of patients in each treatment group and to stratify for known aspects. At the end of the baseline interview and measurements, the primary investigator (F.N.) opened a consecutively numbered opaque envelope containing the patients' group assignment. Participants, research assistant and researcher were no longer blinded for the intervention from this point. However, when performing the analyses the primary investigator was not aware of patients' group assignment.

Patients

A dietician or trained research assistant screened the nutritional status in all elderly patients (≥ 60 years of age, expected length of hospital admission > 2 days) newly admitted to the wards of general internal medicine, rheumatology, gastroenterology, dermatology, nephrology, orthopaedics, traumatology and vascular surgery of the VU University Medical Center, Amsterdam.

Patients were eligible for this study if they were identified malnourished according to the following criteria:

- Body Mass Index (BMI in kg/m^2) ≤ 20 and/or
- 5% unintentional weight loss in the previous month and/or
- 10% unintentional weight loss in the previous six months.

Patients were excluded from the study when they suffered from senile dementia, could not understand the Dutch language or were unable to or willing to give informed consent.

Control group
Patients allocated to the control group received usual care, i.e. they were given nutritional support only on prescription by their treating physician. In general, they did not receive post-discharge nutritional support.

Intervention group
Patients allocated to the intervention group received standardized nutritional support starting in hospital up until three months following discharge:

- Energy and protein enriched diet (during the in hospital period)
- Two additional servings of an oral nutritional supplement (Nutridrink®, Nutricia N.V., Zoetermeer, The Netherlands), leading to an expected increase in intake of 2520 kJ/day (= 600 kilocalories/day and 24 g protein/day (during the entire study period)
- 400 IE vitamin D3 and 500 mg calcium (Calci-Chew D3®, Nycomed bv, Hoofddorp, The Netherlands) per day (during the entire study period)
- Telephone counselling by a dietician in order to give advice and to stimulate adherence to the proposed nutritional intake (every second week following discharge from the hospital, six in total)

Cost measures
Cost data were collected from a societal perspective and measured using two cost diaries, each covering a period of six weeks. Direct health care costs (for example: hospital admission, specialist visits), non-direct health care costs (for example: complementary medicine, informal care) and indirect costs (for example: absenteeism paid and unpaid labour) were included. The cost categories included in the economic evaluation and the prices used were added to Table 3. Dutch standard costs were used to value resource use(18;19). Medication costs were valued using prices of the Royal Dutch Society of Pharmacy(20). Costs of visits to complementary therapists were based on prices from therapists themselves. The cost price of the intervention strategy included oral nutrition support (€ 2.12 per bottle), calcium-vitamin D supplementation (€ 0.30 per tablet) and the telephone counselling by a dietician (€ 44.86 per consultation). These costs were calculated
using a bottom-up approach. Costs of absenteeism from paid work were calculated according to the friction costs approach. The friction cost approach assumes that workers will be replaced after a certain period of sickness absence (friction period). A

friction period of 154 days was used, with mean age and gender-specific incomes of the Dutch population(19). All costs were adjusted to the year 2008 using consumer prices indices(21). Discounting was unnecessary, because neither costs nor benefits were recorded beyond 12 months.

Outcome measures

Trained research assistants and the primary investigator measured outcomes and resource use from patients' admission to the hospital up until three months following discharge. The primary outcome in the economic evaluation was quality of life, measured by the EuroQol (EQ-5D)(22). EuroQol EQ-5D is a standardised instrument to measure health outcome, providing a simple descriptive profile and a single index value for health status. The EQ-5D scores were used to calculate utilities using the Dutch tariff(23). Quality Adjusted Life Years (QALYs) were calculated by multiplying the utilities with the amount of time a patient spent in a particular health state. Transitions between health states were linearly interpolated. The maximum QALY score for a twelve week period is 0.23 (12 weeks follow-up divided by 52 weeks in a year).

Secondary clinical outcomes were physical activities and functional limitations. Both outcomes were measured using two validated questionnaires developed by the Longitudinal Aging Study Amsterdam (LASA): the LASA physical activity questionnaire(24;25) and LASA functional limitations(26;27). The Physical Activity Questionnaire is a face-to-face questionnaire that measures the frequency and duration of, for example, walking outside, sports, and household activities (score 0-6)(25;28). The Functional Limitation Questionnaire measures the degree of difficulties patients experience with 6 activities, for example, climbing stairs and getting up and sitting down in a chair (score 0-6)(26). For a more extensive description of both the physical activities and functional limitations questionnaire, we refer to our previous manuscript(29). In short, an increase in physical activities and a decrease in functional limitations was considered a positive result.

Statistical and economic analyses

Earlier studies have shown that 30% of the elderly hospital population is malnourished at admission. For a clinically relevant difference of 20% in nutritional and a 0.5-point difference in functional status with a statistical significance level of 0.05 and a power of 80%, 2 groups of 80 patients were calculated to be sufficient(17).

Standard descriptive statistical methods were used to express means, standard deviations, percentages, frequencies, changes in variables and minimum and maximum values. Differences in nominal variables between the intervention and control were

tested by chi-square tests. Differences in interval and ratio variables between the groups were tested by independent t-tests.
The statistical analyses for the main analyses were performed according to the intention-to-treat principle. Only patients who died during the study were excluded from the analyses. Multiple imputation was used to impute missing cost and effect data(30). By multiple imputation five imputed data sets were created, each of which was analyzed separately. The results of these five analyses were pooled using Rubin's rules(31).
Costs generally have a highly skewed distribution. Therefore, bootstrapping with 5000 replications was used to estimate "approximate bootstrap confidence" (ABC) intervals around cost differences(32;33).
Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in total costs between the intervention group and control group by the difference in clinical effects. Nonparametric bootstrapping was also used to estimate the uncertainty surrounding the incremental cost-effectiveness and cost utility ratios (5000 replications). The bootstrapped cost-effect pairs were plotted on a cost-effectiveness plane (CE plane)(34) and used to estimate cost-effectiveness acceptability curves (CEA curves). CEA curves show the probability that the intervention is cost-effective in comparison with the control treatment for a range of ceiling ratios. The ceiling ratio is defined as the amount of money society is willing to pay to gain one unit of effect(35).
The 95% confidence intervals were based on two-sided tests.
Statistical analyses were performed using SPSS for Windows, version 16.0 (SPSS, Chicago, USA), Stata/SE, version 10.0 (Stata, Texas, USA) and R, version 2.9.1 (R Development Core Team, Auckland, New Zealand).

Sensitivity analyses
Two sensitivity analyses were performed: in the first one, statistical analyses were restricted to patients with complete follow-up data. The second sensitivity analysis concerned a per protocol analysis, which included only patients who had not used received nutritional support prior the start of the study.

Results
Patient inclusion, patient characteristics and clinical outcomes are extensively described elsewhere(29) and summarized in this manuscript.
We screened 3291 elderly patients on nutritional status, 2716 of which did not meet the malnutrition criteria; 575 patients were malnourished, of which 365 patients were excluded (due to: dementia/confusion (n=114), refused to participate (n=103),

department transfer (n=73), too ill (n=29), not speaking the Dutch language (n=12), no data on malnutrition (n=11), already enrolled in (another) study (n=11) and other reasons (n=12)). There were no differences in gender, BMI and unintentional weight loss between the excluded and the included patients. Patients in the excluded group were significantly older though: 77.4 (SD 9.7) years of age versus 74.6 (SD 9.5), (95% CI 1.1 to 4.4).
In total 210 patients were included in the study; 105 patients in the intervention group and 105 patients in the control group. Mean age was 74.6 (SD 9.5) years (range 60-97 years) and 55.2% of patients were female.
At baseline there were no significant differences in patient and clinical characteristics between the intervention and control group (Table 1).

For 60 patients the follow-up data were incomplete: in the intervention group 16 patients withdrew and 14 patients died, in the control group 19 patients withdrew and 11 patients died. Another 7 patients had missing medication and/or cost data. Thus, complete follow-up on all cost data was available for 143 patients (75 intervention and 68 control patients). Patients without complete follow-up were older; 77.3 (SD 9.5) years of age versus 73.4 (SD 9.3), (95% CI 1.0 to 6.7).

Clinical outcome
Mean length of hospital stay of patients in the intervention group was 13 days (SD 16.8) and in the control group 14 days (SD 12.5) (not statistically significant different (p=0.70, 95% CI -3.2 to 4.8)).
At baseline 30/105 patients (29%) received nutritional support on prescription by their treating physician or dietitian. Three months following hospital discharge this was 23/75 patients (31%).
Table 2 shows the multiply imputed pooled mean effects.
After three months follow-up the multiple imputed pooled mean number of QALYs was 0.15 in the intervention group and 0.13 in the control group (not statistically significant). Also for physical activities no statistically significant difference was observed. For functional limitations, patients in the intervention group improved significantly more than patients in the control group (95% CI -1.2 to -0.3). Three months after the given intervention patients could, for example, dress themselves and climb up a stairs themselves, while patients in the control group were less able.

Table 1: Baseline and clinical characteristics of included patients

Characteristics	Intervention group (n=105)	Control group (n=105)
Female – no. (%)	56 (53.3)	60 (57.1)
Age in yr – mean (±SD)	74.6 (9.7)	74.4 (9.3)
Home situation – no. (%)		
Living alone	54 (51.4)	54 (51.4)
Living with partner / family	51 (48.6)	51 (48.6)
Residence pre-admission – no. (%)		
Living independently	86 (81.9)	90 (85.7)
Nursing home	9 (8.6)	11 (10.5)
Residential home	6 (5.7)	4 (3.8)
Hospital	4 (3.8)	0
Consulting dietician pre-admission – no. (%)	25 (23.8)	23 (21.9)
Use of supplemental drinks pre-admission – no. (%)	23 (21.9)	30 (28.6)
Body Mass Index in categories – no. (%)		
BMI ≤ 20	58 (55.2)	56 (53.3)
BMI 20 – 25	32 (30.5)	39 (37.1)
BMI ≥ 25	15 (14.3)	10 (9.6)
Weight change previous month – no., % (range)	50, -4.5% (-19.8 to 16.9)	46, -4.0% (-35.7 to 17.7)
Weight change previous six months – no., % (range)	48, -9.4% (-30.1 to 16.9)	51, -9.1% (-30.3 to 26.2)
Primary diagnosis in categories – no.(%)		
Acute infections	20 (19.0)	13 (12.4)
Vascular disease	16 (15.2)	16 (15.2)
Kidney insufficiency	13 (12.4)	8 (7.6)
Fractures, orthopaedic disorders	12 (11.4)	10 (9.5)
Malignant neoplasm	10 (9.5)	18 (17.1)
Chronic bowel disease	10 (9.5)	17 (16.2)
Diabetes Mellitus, heart failure and other	10 (9.5)	10 (9.5)
Bleeding in gastrointestinal tract	7 (6.8)	8 (7.6)
Liver, gall and pancreas insufficiency	7 (6.7)	5 (4.9)

There were no significant differences between the intervention group and control group

Table 2: Clinical outcomes after multiple imputation, at three months follow-up in comparison with baseline between the intervention group and control group

Clinical outcome	Intervention group Δ (n=91)	Control group Δ (n=94)	Difference (95% CI)
QALYs [EQ-5D] (n=185)	0.15 (0.01)	0.13 (0.01)	0.02 (-0.01 to 0.02)
Physical activities (n=185)	0.52 (0.17)	0.42 (0.26)	0.10 (-0.53 to 0.73)
Functional limitations (n=185)	-0.47 (0.15)	0.24 (0.15)	**-0.72 (-1.15 to -0.28)**

Data are presented as mean (±SE)

In QALYs and physical activities a positive number is seen as improvement

In functional limitations a negative number is seen as improvement

Health care utilization

Table 3 presents the utilization of health care resources and absenteeism from paid and unpaid work in patients with complete follow-up for costs.

Table 3: Health care utilization of patients to the intervention group or control group in three months following discharge

Type of utilization	Intervention group (n=75)	Control group (n=68)	Difference (CI 95%)	Costs (€) 2008
Direct health care costs				
Medical specialist [no. visits]	3.2 (3.1)	3.0 (2.7)	0.2 (-0.8 to 1.2)	108
Hospital admission ICU included [no. days]	3.1 (7.6)	2.5 (10.5)	0.5 (-3.5 to 2.9)	516 – 1825
Hospital daycare admission [no. days]	1.0 (5.0)	0.8 (4.4)	0.3 (-1.4 to 1.8)	248
Blood test [no. tests]	2.3 (4.3)	1.7 (2.8)	0.6 (-0.4 to 1.9)	15 – 25
Diagnostic research [no. tests] [1]	1.6 (2.0)	1.8 (2.3)	-0.3 (-1.0 to 0.4)	38 – 1112
General practitioner [no. consultations]	1.7 (2.9)	2.8 (3.6)	-1.0 (-2.1 to 0.0)	11 - 44
Paramedic [no. visits] [2]	7.5 (17.7)	5.6 (12.5)	1.9 (-2.4 to 8.3)	25 – 29
Rehabilitation centre [no. days]	0.0 (0.0)	2.4 (13.9)	-2.4 (-10.6 to 5.6)	364
Nursing home [no. days]	2.1 (12.7)	3.3 (12.2)	1.3 (-6.5 to 2.8)	223
Residential home [no. days]	9.0 (22.8)	11.4 (26.4)	2.4 (-7.6 to 0.0)	91
Hospice [no. days]	1.1 (9.7)	0.0 (0.0)	1.1 (0.0 to 6.1)	91
Pharmacy medication [no. doctor's prescriptions]	12.5 (8.2)	16.5 (13.4)	-3.9 (-8.6 to 0.3)	Individual
Professional household home care [no. hours]	17.6 (26.8)	15.2 (52.6)	2.4 (-20.8 to 12.1)	44
Professional physical home care [no. hours]	6.8 (23.6)	8.6 (29.0)	-1.8 (-11.5 to 6.0)	24
Direct non-health care costs				
Complementary medicine [no. visits] [3]	0.3 (1.9)	0.1 (0.7)	0.2 (-0.1 to 0.9)	28 – 68
Informal care [no. hours]	11.4 (61.0)	12.9 (58.6)	-1.5 (-20.1 to 17.8)	9
Indirect costs				
Absenteeism paid labour [no. days]	16.5 (19.3)	47.6 (27.7)	-31.1 (-62.0 to 0.0)	*
Absenteeism unpaid labour [no. days]	2.0 (10.4)	3.6 (15.2)	-1.6 (-6.8 to 2.2)	9

Data are presented as mean (±SD)

[1] Diagnostic research consists of angiography, CT scan, PET scan, MRI scan, X-ray and ultrasound

[2] Paramedic consists of physiotherapist, dietician, Mensendieck therapist, manual therapist, Caecar therapist, occupation therapist and speech therapist

[3] Complementary medicine consists of chiropractor, homeopath, acupuncturist, haptonomic therapist, reiki therapist and foot reflex therapist

[*] Costs based on gender and age of patient

There were no statistically significant differences in health care utilization between the two groups. However, there seemed to be a trend that patients in the control group were more often admitted to other inpatient institutions, while in the intervention group more visits to paramedics were made.

Costs

Table 4 presents the mean (standard error) costs for the intervention group and the control group. Secondary care costs were the largest contributor both to the direct health care costs and to total costs. The mean intervention costs amounted to € 539. Direct non-health care costs and indirect non-health care costs were very similar in both groups. Overall, there were no statistically significant differences in total costs.

Table 4: Total health care costs (in €) and difference in mean total health care costs (95% confidence interval) after multiple imputation, between the intervention group and control group in three months following discharge*

Health care costs	**Intervention group (n=91)**	**Control group (n=94)**	**Difference (95% CI)**
Direct health care costs	8620 (1210)	8217 (1342)	403 (-2783 to 3853)
Primary care costs	343 (95)	283 (46)	61 (-103 to 288)
Secondary care costs	6011 (1155)	6084 (1377)	-74 (-3372 to 3466)
Supportive care costs	1071 (284)	1019 (251)	52 (-705 to 775)
Medication costs	656 (150)	831 (186)	-175 (-594 to 368)
Intervention costs	539 (25)	0 (0)	**539 (483 to 598)**
Direct non-health care costs	154 (72)	115 (59)	38 (-120 to 221)
Complementary medicine	33 (23)	6 (5)	28 (-21 to 76)
Informal care	121 (71)	110 (58)	11 (-136 to 196)
Indirect non-health care costs	356 (133)	352 (176)	4 (-470 to 424)
Costs absenteeism paid labour	321 (133)	221 (169)	99 (-405 to 454)
Costs absenteeism unpaid labour	35 (14)	131 (23)	**-96 (-153 to -36)**
Total direct costs	8773 (1219)	8332 (1345)	441 (-2763 to 3897)
Total indirect costs	356 (133)	352 (176)	4 (-470 to 424)
Total costs	9129 (1227)	8684 (1361)	445 (-2779 to 3938)

Data are presented as mean (±SE)

** 95% confidence interval obtained by bias corrected and accelerated bootstrapping*

Cost-effectiveness and cost-utility analyses

Table 5 presents the results of the cost-effectiveness and cost utility analyses. The difference in QALYs after three months follow-up between intervention and control group was small, leading to a large ICER of € 26962, meaning that € 26962 needs to be invested to gain one additional QALY. For QALYs, most of the bootstrapped cost-effect pairs are located in the north east and south east quadrants (56% and 39% respectively). The accompanying cost-effectiveness acceptability curve shows that for a ceiling ratio of € 20,000/QALY, the probability that the intervention is cost-effective lies around 0.5 (data not shown).

The ICER for physical activities was 4470, meaning that an investment of € 4470 is needed to gain one point on the physical activities scale. The cost-effectiveness acceptability curve (not shown) showed that the probability that the intervention is cost-effective in comparison with usual care was 0.6 at max.

For functional limitations a significant difference in effects, but not for costs, was observed. The ICER for improvement in functional limitations was € 618, meaning that one point improvement extra in the intervention group costs € 618 extra in comparison with the control group.

The cost-effectiveness plane in Figure 1 shows that most bootstrapped cost-effect pairs for functional limitations were located in the north east and south east quadrants (59% and 41% respectively). This means that the intervention was effective (cost-effect pairs located on the right side of the Y-axis) and that costs were distributed both in the more costly (north east) and less costly (south east) quadrant. The cost-effectiveness acceptability curve in Figure 2 shows the probability that the intervention is cost-effective in comparison with the control treatment for a range of ceiling ratios. The ceiling ratio is defined as the amount of money society is willing to pay to gain one unit on the functional limitation scale (0-6 points). In this study, this means that, if society is willing to invest € 6500, there is a 0.95 probability that the intervention is cost-effective in comparison with usual care.

Table 5: Results of cost-effectiveness and cost-utility analyses

Analysis	Sample size		Outcome	Cost difference (€)	Effect difference	ICER	Distribution CE plane			
	I	*C*		*(95% CI)*	*(95% CI)*		*NE*	*SE*	*SW*	*NW*
Main analysis	91	94	QALY	445 (-2779 to 3938)	0.02 (-0.00 to 0.04)	26962	56%	39%	1%	4%
	91	94	PA	445 (-2779 to 3938)	0.1 (-0.53 to 0.73)	4470	37%	26%	14%	23%
	91	94	FL	445 (-2779 to 3938)	-0.72 (-1.15 to -0.28)	-618	59%	41%	0%	0%
Complete case analyses	69	67	QALY	330 (- 2703 to 3672)	0.02 (0.00 to 0.05)	13581	56%	43%	0%	1%
	54	50	PA	1842 (-846 to 5383)	0.05 (-0.48 to 0.61)	37119	50%	7%	4%	39%
	68	66	FL	-97 (-3480 to 3132)	-0.47 (-0.94 to -0.03)	-204	47%	51%	0%	2%
Per protocol analysis	64	61	QALY	-2188 (-5912 to 1301)	-0.01 (-0.03 to 0.02)	314808	2%	25%	63%	10%
	64	61	PA	-2188 (-5912 to 1301)	-0.08 (-0.85 to 0.70)	27804	4%	39%	49%	8%
	64	61	FL	-2188 (-5912 to 1301)	0.07 (-0.49 to 0.63)	-31658	3%	37%	52%	8%

I = intervention group, C = control group, PA = physical activity, FL = functional limitations
NE = more costly, more effective, SE = less costly, more effective, SW = less costly, less effective, NW = more costly, less effective

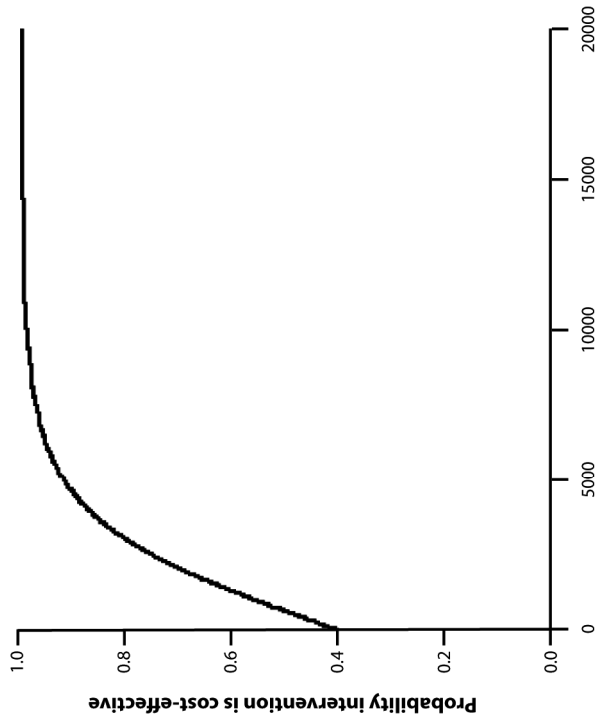

Figure 2: Cost-effectiveness acceptability curve for functional limitations

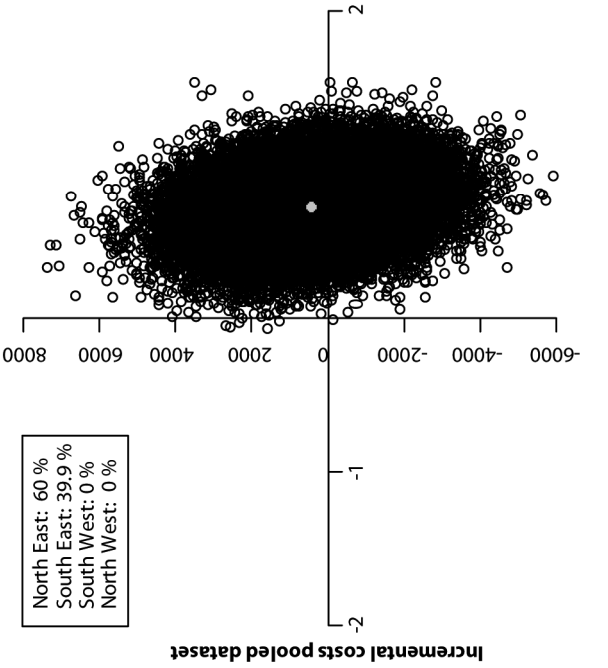

Figure 1: Cost-effectiveness plane for the difference in functional limitations

Sensitivity analyses

Results of complete case and per protocol analyses are also presented in Table 5. In the complete case analyses, there were no significant differences in costs. Again, there was a statistically significant difference in functional limitations between intervention and control patients in favour of the intervention group, and again differences in QALYs and physical activities did not differ significantly between groups. The CEA curves showed that substantial amounts of money should be invested to reach a 0.95 probability that the intervention is cost-effective with control (curve not shown).

In the per protocol analyses, effects were small and not statistically significantly, but in this analysis costs in the intervention group were substantially lower than in the control group, although this difference was not statistically significant. Cost-effectiveness analyses showed that the intervention strategy was not cost-effective in comparison with the control treatment.

Discussion

The main finding in this randomized controlled trial is that a multi-component nutritional intervention, consisting of oral nutritional supplements and calcium/vitamin D supplementation, supported by dietetic counselling, for malnourished elderly from hospital admission until three months following discharge, is effective and cost-effective for functional limitations. For quality of life and physical activities this was not the case. All these results were confirmed by sensitivity analyses.

Functional limitations

Prevention of disability and preservation of independence is one of the most important goals in the (medical) treatment of elderly individuals. Therefore, the decrease in functional limitations in patients receiving the nutritional intervention is thought to be of great importance, more than a gain in body weight. In daily practice this means that patients can climb a stairs again, or dress themselves without needing help, thus contributing to improved functional independence.

Literature

Other literature on functional outcomes is scarce, and often of poor quality(16), yet this literature confirms our findings. With respect to quality of life, studies comparable to ours by Edington et al.(36) and McMurdo et al.(37), were also negative following eight weeks of nutritional support. Other studies failed to show beneficial effects of nutritional intervention on physical activities(38) following eight weeks of nutritional supplementation or on body weight even after six months(39). The study by Woo et

al.(40) was the only one to confirm significant improvements in functional limitations after oral nutritional supplements.

Cost-effectiveness

Our study results indicate that a € 6500 investment is necessary to reach a 95 percent chance of improvement of functional limitations. In The Netherlands, an investment of below € 20000 is regarded cost-effective. These interventions are being considered for implementation by health care policy makers. Moreover, the incremental costs of the intervention can probably be considerably reduced in the future. A university dietician is more expensive than a community dietician; and hypothetically costs can also be saved on packaging (larger volumes) and delivering (house brands sold in the supermarket, instead of industry brands sold in the pharmacy) of oral nutritional supplements.

Because we measured costs from a societal perspective, direct health care costs, non-direct health care costs and indirect non-health care costs were measured. For measuring quality of life we used the EuroQol (EQ-5D). A systematic review on QALYs showed that the EuroQol, with 47.5% of the studies, the most frequent used tool was for this goal(41). By including the EuroQol in this study, we tried to contribute to the comparability of cost-effectiveness studies.

We are aware of only one other randomized controlled trial on costs and benefits of oral nutritional supplements in the community, by Edington et al.(36). In this trial, costs were summarized and compared between groups by t-tests. No health-economic benefits of oral nutritional supplements were observed, neither were any positive effects on functional outcomes or quality of life found. Cost-effectiveness ratios were not presented. Therefore, we carefully conclude that our trial is the first one calculating costs in relation to effects.

Adherence

We had good adherence on data, which is in contrast to the trial by McMurdo et al.(37), a trial very similar to ours. Adherence to oral nutritional supplements and telephone counselling by dietician was 80% and 96% respectively, which is much higher than in many of the previous studies. We hypothesize that the dietitian has played an important role in the excellent adherence to the supplements and, thus, to the positive outcomes.

This study does not report on changes in weight or nutritional intake between groups. It may be hypothesized that our patients substituted their normal diet with oral nutritional supplements without effectively increasing their dietary intake. We have studied these data and found that patients in the intervention group increased their nutritional intake significantly more than those in the control group. Intervention patients also gained more weight than control patients(29). We therefore conclude that the positive results

reported in this manuscript are attributable to the increase in intake and not to other effects.

Setting
Our study took place in a relatively small university hospital in Amsterdam. The results found in this study are likely to apply to other hospitals in The Netherlands as the patients included were not admitted for 'academic' indications but rather for quite normal indications (Table 1).

Loss to follow-up
By the end of the study, 28.5% of our patient population was lost for follow-up, due to death or withdrawal, i.e. the most severely ill patients. However, the withdrawals were equally divided between control patients and intervention patients. We, therefore, do not think that this may have biased the study results.

Strengths
One of the strengths of this study is that it was a randomized controlled trial, including malnourished patients only, with properly concealed allocation and intention-to-treat analyses. Also, this study focussed on primary outcomes of relevance (i.e. quality of life, physical activities and functional limitations), rather than on weight changes only.

Study limitations
Our study does have some limitations. First, the follow-up period of this study was three months only. It can be questioned whether a follow-up period of three months is long enough to find effects on quality of life and physical activities.
Milne et al.(16) summarize in their review that the intervention time of their reviewed studies is often too short to have a realistic chance of detecting differences in morbidity, functional status or quality of life. They strongly suggest that future trials should have sufficient statistical power and length of follow-up to be able to detect any beneficial effects. We have no indication yet how long the ideal intervention period should be, yet six months sounds plausible.
In our earlier manuscript(29), we have shown moderate gain in weight and fat-free mass in the intervention group, especially in men. We hypothesize that the order of effects is weight gain first, then improvement in physical activities (based on improvements in fat-free mass) and finally increased quality of life. If this is true, a trial with a longer follow-up period should confirm these results.
Second, our study was powered to detect differences in functionality, but underpowered to detect cost differences. This is reflected by the wide confidence

intervals around the cost differences. This is a common problem in economic evaluations alongside clinical trials. Because of the heavily skewed distribution data, very large numbers of patients are needed to detect relevant cost differences(42). This adds to the arguments of Milne et al. to perform a large intervention trial (with longer follow-up).

Finally, 25 patients died during the three months follow-up and another 35 patients withdrew after inclusion, partly because of terminal illness. A more detailed patient selection at baseline, identifying patients in whom malnutrition is and indication of end-stage disease, rather than an indication of a deplored nutritional status, could possible add to the effectiveness of the intervention.

Conclusion

This study shows that post-discharge multi-component nutritional support (supplementation of energy, protein, calcium and vitamin D, supported by dietetic counselling) improves functional limitations, but not quality of life or physical activities, in comparison to usual care. Cost-effectiveness analyses show that the intervention is cost-effective for functional limitations as well, after a follow-up period of only three months.

Future research should replicate the findings of our study. We suggest to extend the follow-up period to at least six months, among a larger, less old, ill and frail patient group and among the younger working elderly population. These adaptations can possibly show higher profits on costs and effects.

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CHAPTER 5

Short-term oral nutritional intervention with protein and vitamin D decreases falls in malnourished elderly patients

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Short-term oral nutritional intervention with protein and vitamin D decreases falls in malnourished older adults
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Abstract

Background

The aim of this randomized controlled trial is to evaluate the effects of a short-term nutritional intervention with protein and vitamin D on falls in malnourished elderly patients.

Methods

This randomized controlled trial included hospital admitted malnourished elderly (≥ 60 year) patients. Patients in the intervention group received nutritional supplementation (energy and protein enriched diet, oral nutritional supplements, calcium-vitamin D supplement, telephone counselling by a dietician) up until three months following discharge from hospital. Patients in the control group received usual care. Primary outcomes were number of patients who fell, fall incidents, serum 25-hydroxyvitamin D, and dietary intake. Measurements were performed on admission to hospital and three months following discharge.

Results

Three months following discharge, 10 patients (10%) in the intervention group had fallen at least once, compared with 24 (23%) in the control group (hazard ratio 0.41, 95% confidence interval (CI) 0.19 to 0.86). There were 57 fall incidents (16 in the intervention group; 41 in the control group). A significantly higher intake of energy (280 kcal, 95% CI 37 to 524 kcal) and protein (11 g, 95% CI 1 to 25 g) and significantly higher serum 25-hydroxyvitamin D levels (10.9 nmol/L, 95% CI 2.9 to18.9 nmol/L) were found in patients in the intervention group than in controls.

Conclusion

A short-term nutritional intervention consisting of oral nutritional supplements and calcium and vitamin D supplementation and supported by dietetic counselling in malnourished elderly patients decreases the number who fall and fall incidents.

Background

Falls are a common and serious cause of morbidity and mortality in elderly people. Fractures as a result of falls lead to enormous healthcare costs(1). Each year, one in three community-dwelling persons aged 65 and older experiences at least one fall(2-4). Loss of muscle mass and strength are regarded as important risk factors for falls, functional decline, and disability(5).

Vitamin D deficiency(6) and malnutrition(7) can decrease muscle mass and muscle strength. In well-nourished community living elderly people at risk of vitamin D deficiency, vitamin D supplementation has been shown to improve muscle strength, function, and balance in a dose-related pattern(8). These benefits translate into a reduction in falls, as shown in epidemiological studies and randomized clinical trials. Several meta-analyses in healthy persons support the beneficial effects of vitamin D supplementation on falls(9;10).

Malnutrition is also associated with a higher incidence of falls(11;12). Although a nutritional intervention in malnourished elderly people has been shown to accelerate weight gain(13), only a few studies have shown an increase in muscle mass(14) or improved muscle function(15;16). One study in frail elderly people showed a reduction in the number of falls following 12 weeks of oral nutritional supplements(17).

A recent study of a nutritional intervention in malnourished elderly people (3 months of oral nutritional supplements (ONS), calcium and vitamin D supplementation, and dietetic counselling) induced weight gain and a decrease in functional impairment(18). The aim of the current study was to assess the effects of the same intervention on fall incidents.

Methods

Design

The current study is a secondary analysis of a previously conducted study that has been reported elsewhere(18). The primary study was a randomized controlled trial comparing ONS, calcium and vitamin D supplementation, and dietetic counselling with usual nutritional care in malnourished elderly patients from hospital admission up until three months following discharge. The primary outcome was changes in activities of daily living (functional limitations, physical performance, and physical activity). Secondary outcomes included changes in body weight, body composition, and muscle strength. Details about the design have been described more extensively elsewhere(19). This secondary analysis focuses on falls.

The study design was in accordance with the Declaration of Helsinki and was approved by the Medical Ethics Committee of the VU University Medical Center, Amsterdam.

Patients
All elderly patients (aged ≥ 60) newly admitted (expected length of hospital stay > 2 days) to the departments of general internal medicine, rheumatology, gastroenterology, dermatology, nephrology, orthopaedics, traumatology, and vascular surgery of the VU University Medical Center were screened for malnutrition.
Patients were eligible for the study if they were identified as being malnourished according to the following criteria: body mass index (BMI) of 20.0 kg/m^2 or less, 5% or more self-reported unintentional weight loss in the previous month, or 10% or more self-reported unintentional weight loss in the previous 6 months.
Patients with dementia were excluded if this diagnosis was documented in the hospital record or in a referral letter from the patients' primary care or nursing home physician.

Randomization
A computerized random number generator was used to assign patients in blocks of 10 to the control or intervention group. At the end of the baseline interview and measurements, the primary investigator (F.N.) opened a consecutively numbered opaque envelope containing the patient's group assignment. Patients, research assistants, and researchers were aware of group assignment during the intervention phase. Prior to analysis, the primary investigator received an anonymized data set and was no longer aware of group assignment. A second independent researcher also entered all data on falls into the database. No differences between researchers were found for identifying fall incidents.

Control group
Patients allocated to the control group received usual care (given nutritional support only on prescription from their treating physician). In general, they did not receive post-discharge nutritional support.

Intervention group
Patients allocated to the intervention group received standardized nutritional support from hospitalization up until three months following discharge.

- Energy- and protein-enriched diet (during the in-hospital period). This diet excludes low-fat products and includes whole milk products, butter or margarine, and energy-and protein-enriched porridge and desserts. The porridge and desserts were fortified with extra cream and carbohydrates

(maltodextrins). Patients were also offered one energy- and protein-enriched snack (containing approximately 250 kcal and 10 g protein) each day. This diet provided intake of approximately 750 kcal and 30 g of protein more per day than the regular hospital menu.

- Two additional servings per day of an ONS (Nutridrink®, Nutricia, N.V., Zoetermeer, The Netherlands) were offered. This was intended to provide an additional 600 kcal, 24 g of protein, 176 IU of vitamin D3, and 364 mg of calcium per day during the entire study period. ONS were first dispensed for 2 weeks (2 bottles per day × 14 days = 28 bottles) and subsequently for 4 weeks (2 bottles per day × 28 days = 56 bottles). The dietitian ordered the first batch of ONS. During telephone counselling, the dietitian asked the patient how many bottles of ONS had been consumed during the past 2 weeks. If necessary, the dietitian reminded the patient to order new ONS. After the first 2 weeks, patients (or family) ordered more by telephone from the pharmaceutical delivery service center. When patients (or their family) were unable to order themselves, the dietitian ordered for them.
- 400 IU vitamin D3/day and 500 mg calcium per day during the entire study period, which in The Netherlands is usually given as a combined calcium and vitamin D supplement (Calci-Chew D3®, Nycomed bv, Hoofddorp, The Netherlands).
- Telephone counselling by a dietitian was conducted every second week following hospital discharge (six sessions in total) to encourage adherence to the prescribed supplements. During the telephone consultation, the patient's general health status and any difficulties with the prescribed diet and supplements were discussed. For example, patients were asked how many of the prescribed ONS they had consumed during the past 2 weeks. If the intake of ONS was less than two bottles per day, patients were asked whether they (dis)liked the taste, were advised not to take the ONS just before a meal, were given recipes to try with the ONS, and were advised to order other flavours of ONS at the pharmaceutical service center. All patients had access to a telephone.

If patients took all of the prescribed supplements following discharge, this would provide an additional 600 kcal, 24 g of protein, 576 IU of vitamin D3 and 864 mg calcium per day.

Adherence

The interviews to recall adherence to ONS and calcium and vitamin D supplementation were conducted by telephone every other week. Patients did not have to keep a written record of their supplement use. The dietitian asked patients about their total supplement intake in the past 2 weeks and checked this with the deliveries from the pharmaceutical service center or pharmacy.

Monitoring adherence

- *Dietary intake*

Dietary intake was recorded in a diary on admission to the hospital and again three months following discharge. On each occasion, seven meals or snacks (breakfast, in between morning, lunch, in between afternoon, dinner, in between evening, night) were recorded. Average daily intake of food and drinks during the past 2 weeks was documented.

Dietary energy (kcal/d) and protein (g/d) intake were calculated using a nutrition analysis software application with the use of the most recent Dutch Food Composition table(20).

- *Serum 25-hydroxyvitamin D*

For measurement of 25-hydroxyvitamin D, serum was kept frozen at −20°C until analysis at the Endocrine Laboratory of the VU University Medical Center. One sample was collected at baseline and the other one 3 months following discharge. Both samples from each patient were analyzed together in one run to minimize variation within patients; 25-hydroxyvitamin D in serum was analyzed using radioimmunoassay (Diasorin, Stillwater, MN, USA). The interassay coefficient of variation was 10%.

The Health Council of The Netherlands advises levels of 50 nmol/L or above to improve bone quality and reduce the risk of fracture and falling in elderly people(21).

Outcome parameters

- *Measurements*

All measurements were made at baseline (within 3 days following hospital admission) and again three months following hospital discharge. Measurements of fat-free mass, hand grip strength, and physical activity were part of the parent study. Assessment of falls was part of the secondary analysis.

- *Fat-free mass and hand grip strength*

Bioelectrical impedance spectroscopy (BIS) was used to determine changes in fat free mass (kg)(22;23). Measurements were performed using an ECF/ICF Bio Impedance Spectrum Analyzer, Hydra 4200 (Xitron Technologies, San Diego, CA, USA).

Hand grip strength (kg) was measured using a hydraulic hand dynamometer (Baseline, Fabrication Enterprises, Inc., Elmsford, NY, USA)(24). Patients were asked to perform two maximum force trials with their non-dominant hand in a standing position and, if not possible, from a seated position. The highest value was used.

- *Physical activities, functional limitations, and physical performance*

Physical activity was assessed using the validated Longitudinal Aging Study Amsterdam Physical Activity Questionnaire, which includes questions on walking, cycling, light and heavy household activities, gardening, and sports (yes=1 point, no=0 points). Total score was calculated by summing the scores of all activities, ranging from 0 (does not have difficulty with any of the activities) to 6 (has difficulty with all activities)(25).
Functional limitations were assessed using the validated LASA Functional Limitations questionnaire as the degree of difficulty that patients experienced with six activities (e.g., climbing stairs and getting up from and sitting down in a chair. Patients scored between 0 and 6 points; lower scores indicate less functional limitation(26;27).
Physical performance was assessed using the validated LASA Physical Performance questionnaire, which includes three tests: timed walk test, chair-stand test, and tandem stand(28). Patients scored between 0 and 12 points (4 points for each test); lower scores indicate poorer physical performance.

- *Fall incidents*

Patients recorded their falls weekly. A fall was defined as an unintentional change in position resulting in coming to rest at a lower level or on the ground(29). The time of recording was documented in the fall diary. Patients were asked to return their first diary by mail 6 weeks following discharge from hospital. When it was not received within 1 week after week 6, patients were telephoned and reminded to send it. In a few cases, sending back the diary was not possible, and the information on falls was obtained over the telephone. This procedure was repeated for the second fall diary covering the period 7 to 12 weeks after discharge. The described procedure of collecting data on fall incidents has been shown to be valid and reliable in earlier studies(18).

Statistical methods

Differences in dichotomous variables between the intervention and control groups were tested using chi-square tests. Differences in continuous variables between the groups were tested using independent t-tests. These tests were performed for baseline and follow-up measurements. The statistical analyses for the main outcome parameters were restricted to patients with complete follow-up. For skewed data (number of fall incidents) a nonparametric test (Mann Whitney U) was used.

Logistic regression analysis was used to evaluate the difference in falling (yes or no) between the intervention and control groups. A time-to-event analysis was performed calculating a hazard ratio using Cox regression, log rank, and a Kaplan-Meier curve.
The presence of effect modification and confounding was investigated. Hazard ratios with accompanying 95% confidence intervals (for differences in means) and *p*-values are presented. Chi-square tests were applied to compare numbers of patients with vitamin D levels at different cut-off points. Statistical significance was defined as $P \leq .05$. Statistical analyses were performed using the SPSS for Windows, version 16.0 (SPSS, Inc., Chicago, IL, USA).

Results

Patient inclusion, patient characteristics, and clinical outcomes have been described extensively elsewhere(18). In summary, 210 patients were included in the study: 105 randomized to the intervention group and 105 to the control group (Figure 1).
Seventeen percent of the 3,291 patients screened for inclusion in the study were identified as malnourished; 55% of the malnourished patients had a BMI less than 20.0 kg/m^2, and 23% had a BMI below 18.5 kg/m^2. Seventeen percent of patients reported more than 10% weight loss over the last month (acute weight loss) and 49% had more than 10% weight loss over the last 6 months.
Follow-up data were incomplete for 60 patients; in the intervention group, 16 withdrew and 14 died, and in the control group, 19 withdrew and 11 died. Patients without complete follow-up were older than those with complete follow-up (77.3 ±9.5 versus 73.4 ±9.3, 95% CI 1.0 to 6.7).
No significant differences between the intervention and control groups were observed at baseline for functional limitations, body weight, grip strength, and physical performance, all of which are known potential predictors of falling (Table 1).
At baseline, 30 of 105 (29%) patients in the control group and 23 of 105 (22%) in the intervention group were receiving nutritional support with a prescription from their treating physician or dietitian. Three months following hospital discharge, 23 of 75 (31%) and 63 of 75 (84%) patients, respectively, were receiving such nutritional support.
For the primary outcome parameters, a trend toward greater body weight and fewer functional limitations was observed in patients receiving nutritional intervention than in those receiving usual care (18).

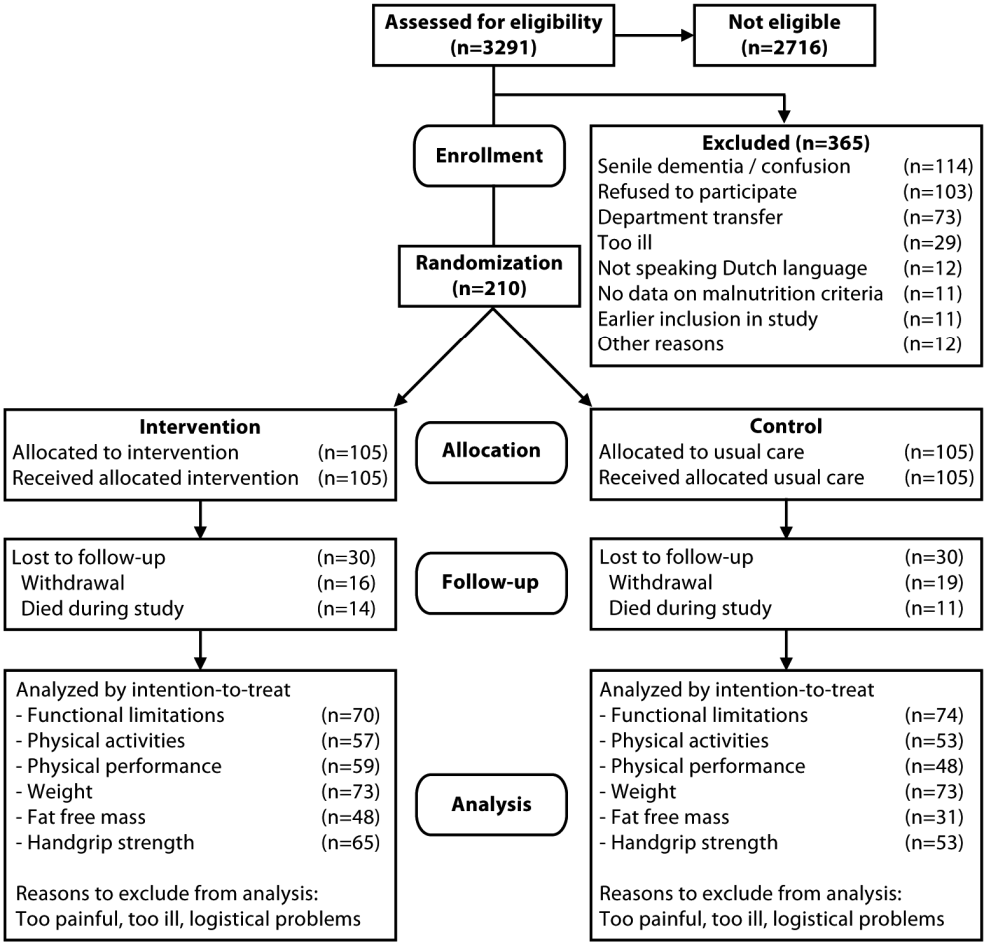

Figure 1: The CONSORT flow chart

Table 1: Baseline and clinical characteristics of included patients

Characteristics	**Intervention group (n=105)**	**Control group (n=105)**	***p*-value**
Gender – no. females (%)	56 (53.3)	60 (57.1)	0.579
Age, y – mean (±SD)	74.6 (9.7)	74.4 (9.3)	0.879
Home situation – no. (%)			1.000
Living alone	54 (51.4)	54 (51.4)	
Living with partner / family	51 (48.6)	51 (48.6)	
Residence pre-admission – no. (%)			0.196
Living independently	86 (81.9)	90 (85.7)	
Nursing home	9 (8.6)	11 (10.5)	
Home for the elderly	6 (5.7)	4 (3.8)	
Hospital	4 (3.8)	0	
Consulting dietician pre-admission – no. (%)	25 (23.8)	23 (21.9)	0.742
Use of supplemental drinks pre-admission – no. (%)	23 (21.9)	30 (28.6)	0.266
Body Mass Index in categories – no. (%)			
BMI ≤ 20	58 (55.2)	56 (53.3)	0.251
BMI 20 – 25	32 (30.5)	39 (37.1)	0.991
BMI ≥ 25	15 (14.3)	10 (9.6)	0.143
Weight change last month – % (range)	-4.5 (-19.8 to 16.9)	-4.0 (-35.7 to 17.7)	0.422
Weight change last six months – % (range)	-9.4 (-30.1 to 16.9)	-9.1 (-30.3 to 26.2)	0.616
Medical specialty – no. (%)			0.314
Surgical			
Traumatology	7 (6.7)	3 (2.9)	
Vascular surgery	13 (12.4)	16 (15.1)	
Non surgical			
Internal medicine	32 (30.5)	43 (41.0)	
Gastroenterology	30 (28.6)	30 (28.6)	
Nephrology	14 (13.3)	8 (7.6)	
Rheumatology	5 (4.8)	4 (3.8)	
Dermatology	4 (3.7)	1 (1.0)	
Primary diagnosis in categories – no. (%)			0.499
Acute infections	20 (19.0)	13 (12.4)	
Vascular disease	16 (15.2)	16 (15.2)	
Kidney insufficiency	13 (12.4)	8 (7.6)	
Fractures, orthopaedic disorders	12 (11.4)	10 (9.5)	
Malignant neoplasm	10 (9.5)	18 (17.1)	
Chronic bowel disease	10 (9.5)	17 (16.2)	
Diabetes Mellitus, heart failure and other	10 (9.5)	10 (9.5)	
Bleeding in gastrointestinal tract	7 (6.8)	8 (7.6)	
Liver, gall and pancreas insufficiency	7 (6.7)	5 (4.9)	
Hand grip strength (kg) – mean (±SD)	17.9 (9.1)	17.9 (8.0)	0.930

Table 1: (continued)

Characteristics	Intervention group (n=105)	Control group (n=105)	*p*-value
Physical activities (0-6 points) – mean (±SD)	1.7 (1.3)	1.4 (1.3)	0.227
Functional limitations (0-6 points) – mean (±SD)	1.9 (2.0)	1.8 (1.9)	0.735
Physical performance			
Total score (0-12 points) – mean (±SD)	3.1 (4.2)	2.8 (4.0)	0.614
Walking time (0-4 points) – mean (±SD)	1.1 (1.5)	1.1 (1.4)	0.779
Chair-stand (0-4 points) – mean (±SD)	0.8 (1.4)	0.8 (1.3)	0.604
Tandem stand (0-4 points) – mean (SD)	1.1 (1.7)	1.0 (1.7)	0.133
Kcal intake (kcal/d) – mean (±SD)	1473 (625)	1462 (615)	0.896
Protein intake (g/d) – mean (±SD)	52 (27)	54 (29)	0.603
Protein intake g/kg/d – mean (±SD)	0.9 (0.5)	0.9 (0.6)	0.398
Protein intake <0.8 g/kg/d – no. (%)	46 (49)	41 (43)	0.392
Serum vitamin D level (nmol/l) – mean (±SD)	39.8 (19.3)	42.5 (21.8)	0.391
Serum vitamin D level ≥ 50 nmol/l – no. (%)	21 (20)	32 (30)	0.081

Monitoring adherence

Results on intake and serum 25-hydroxyvitamin D are shown in Table 2.

Energy and protein intake and serum 25-hydroxy vitamin D levels were significantly higher in the intervention group than in the control group.

Table 2: Energy, protein and serum 25-hydroxyvitamin D between intervention group and control group after three months follow-up and the difference between baseline and follow-up

Characteristics	Intervention group		Control group		Difference in Δ (*p*-value)
	End n=75	End-baseline	End n=75	End-baseline	
Kcal intake (kcal/d) – mean (±SD)	2152 (752)	595 (753)	1766 (661)	315 (640)	**280 (*p*=0.002)**
Protein intake (g/d) – mean (±SD)	78 (34)	21 (29)	63 (30)	10 (29)	**11 (*p*=0.040)**
Protein intake (g/kg/d) – mean (±SD)	1.3 (0.5)	0.3 (0.4)	1.0 (0.5)	0.1 (0.5)	0.2 (*p*=0.074)
Protein intake <0.8 g/kg/d – no. (%)	10 (16)	-	21 (30)	-	**(*p*=0.049)**
Serum vitamin D level (nmol/l) – mean (±SD)	65.7 (25.5)	24.0 (20.3)	54.8 (25.4)	13.1 (17.3)	**10.9 (*p*=0.008)**
Serum vitamin D level ≥ 50 nmol/l – no. (%)	32 (37)	-	23 (47)	-	(*p*=0.301)

Δ = improvement intervention - control

Adherence to ONS, vitamin D supplementation, and dietetic counselling was 80%, 96%, and 96%, respectively. Eighty percent of patients in the intervention group consumed ONS, with a mean intake of 1.6 bottles per day (target 2/day). Ninety-six percent of patients in the intervention group consumed the calcium and vitamin D supplement, with a mean intake of 0.9 tablets per day (target 1/day). The dietitian contacted 96% of patients by telephone, with a mean of 5.8 contacts (target 6 contacts during three months follow-up).
Results of adherence to ONS and vitamin D supplementation as reported by patients compared well with distribution data from the pharmaceutical service center and patients' pharmacies.

Body weight and BMI
Body weight and BMI at baseline are presented in Table 1.
Three months following discharge, body weight increased to 64.7 kg (± 14.4) in the intervention group and 61.0 kg (± 12.2) in the control group. Three months following discharge, the mean difference between the groups was 3.7 kg (95% CI -0.6 to 8.1).
BMI increased to 22.1 kg/m^2 (± 4.5) in the intervention group and 21.0 kg/m^2 (± 3.7) in the control group. Three months following discharge, the mean difference between the groups was 1.1 kg/m^2 (95% CI -0.3 to 2.4.)

Fat-free mass and hand grip strength
Neither fat-free mass nor hand grip strength changed significantly from baseline in the intervention or the control group. Mean increase in fat free mass was 3.3 kg (± 4.3) in the intervention group and 2.8 kg (± 4.1) in the control group (95% CI -1.5 to 2.4). Mean increase in grip strength was 0.2 kg (± 5.6) in the intervention group and 1.0 kg (± 6.7) in the control group (95% CI -3.0 to 1.5).

Physical activities
Physical activities did not change significantly in the intervention or control group. Mean improvement in score was 0.5 (± 1.5) in the intervention group and 0.6 (± 1.5) in the control group (95% CI -0.7 to 0.5).

Fall incidents
Results on fall incidents are shown in Table 3.
Patients in the control group fell more than twice as often as patients in the intervention group. In total, 57 fall incidents occurred: 16 in the intervention group and 41 in the control group. Ten patients (10%) in the intervention group and 24 (23%) in the control

Table 3: Patients who fall and fall incidents after three months follow-up in malnourished elderly patients

	Intervention group	Control group	Effect
Patients who fall			
Total number (%) of patients who fall	10 (10)	24 (23)	**0.41 (*p*=0.018)***
Mean number of fall incidents (SD)			
Among the whole group (n=I:76 / C:75)	0.21 (0.57)	0.55 (0.84)	**0.001#**
Among patients who fall (n=I:10 / C:24)	1.6 (1.1)	1.7 (0.91)	0.550#

I, intervention group; C, control group

**, Hazard ratio (p-value)*

#, Mann Whitney U

group had one or more fall incidents (HR 0.41, 95% CI 0.19 to 0.86, p=0.02, log rank); 56% of patients in the intervention group and 68% of those in the control group who had fallen had more than one fall incident (not significantly different). The mean number of falls per patient in patients who had fallen was 1.6 (± 1.1) in the intervention group and 1.7 (± 0.9) in the control group. This was not significantly different between groups (p=0.55). In 94% of fall incidents, patients fell in their home, and only one patient (in the control group) reported a fracture following a fall incident. Figure 2 shows a Kaplan-Meier curve for the time (days) to a fall incident for patients in the intervention group versus patients in the control group.

Confounding or effect modification was not observed for age, sex, body weight, BMI (≤ 20.0 versus > 20.0 kg/m^2), unintentional weight loss in the previous month, unintentional weight loss in the previous 6 months, fat-free mass, hand grip strength, physical activities, functional limitations, or physical performance.

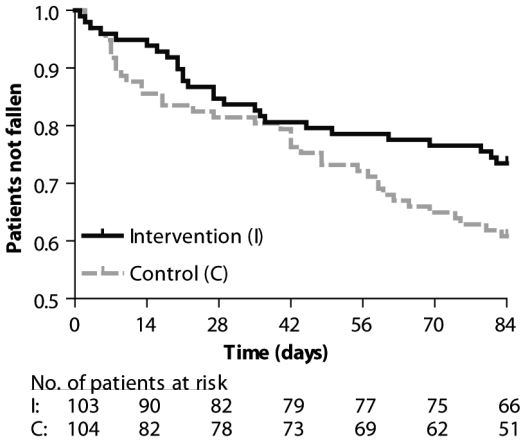

Figure 2: Kaplan-Meier curve for the time (days) to a fall incident for patients in the intervention group versus patients in the control group

Discussion

A short-term nutritional intervention, consisting of oral nutritional supplements and vitamin D supplementation, supported by dietetic counselling, decreases the number of patients with falls and fall incidents in malnourished elderly patients. There were no statistically significant differences in physical activity between the groups.

Approximately 30% of community-dwelling persons aged 65 and older fall once a year, and 15% fall at least twice a year(30-32). The occurrence of falls in intervention patients (10% in 3 months) was as expected. In contrast, the occurrence of falls in the control group (30% in 3 months) was higher than expected.

Because this study was designed as a secondary analysis of a parent study, data were not collected on all well-known risk factors for falling, but no significant differences were observed between intervention patients and controls for functional limitations, body weight, grip strength, and physical performance. Data were not collected on, for example, poly-pharmacy or vision impairment, other well-known risk factors that could have influenced the results. It can be assumed that the randomized design of the trial accounted for similar distribution of all fall risk factors between the groups.

A recent meta-analysis of randomized clinical trials showed that serum 25-hydroxyvitamin D concentrations of 60 nmol/L or higher were associated with fewer falls, and lower concentrations were not(33). A study of a sample of the Longitudinal Aging Study Amsterdam (LASA) cohort found that a serum 25-hydroxyvitamin D level less than 30 nmol/L was associated with a higher fall incidence than a higher level(34). In the present study, patients' mean serum 25-hydroxyvitamin D levels were inadequate in both groups at baseline. After the intervention period, serum 25-hydroxyvitamin D levels in both groups had improved, more so in the intervention group than in the control group. In the intervention group, mean serum level reached 65 nmol/L, which is above the 50 nmol/L that the Institute of Medicine(35) and the Health Council of The Netherlands(21) have suggested. Still, 37% of all patients in the intervention group did not reach a serum 25-hydroxyvitamin D above the threshold of 50 nmol/L, even after supplementation.

The study was conducted with a low-dose vitamin D (400 IU/d from calcium and vitamin D supplementation and 176 IU/d from ONS). After the start of this study in 2006, the dose of vitamin D supplementation advised by the Health Council of The Netherlands for elderly people increased to 800 IU/d(21). It is possible that a higher dose of vitamin D would reduce fall incidence even further. Further research in a study with a dose-response design is needed.

When studying the absolute number of patients with levels less than 30 nmol/L or less than 50 nmol/L, there were no significant differences between groups at baseline or at three months follow-up. This supports the idea that the combined intervention, rather

than only the vitamin D, was effective in the reduction of falls. The intervention consisted of a combination of energy, protein, vitamin D, and calcium. In addition, a dietitian counselled patients every other week. This study does not give an answer to which specific nutritional component or combination of components and counselling is responsible for the effects found.

Falling is associated with activity pattern, muscle mass, and strength. Increasing physical activity was not a primary aim of this study. Reported activity levels were measured using a questionnaire. They did not change in the intervention group or the control group, suggesting that changes in activity level did not account for the difference in falls.
The results of the present study did not confirm an increase in falls because of decreased muscle mass and strength. Measurements of muscle mass (using bioelectric impedance) and strength (using handgrip dynamometry) were crude and probably not sensitive enough to pick up small changes. Nevertheless, function improved(18). Results may be ascribed to changes in neuromuscular function rather than to changes in muscular strength. A vitamin D supplementation study showed neuromuscular improvements following a short-term intervention (16 weeks), which confirms that neuromuscular improvements may take place over a short period of time(36).

One of the strengths of this study is that the adherence to the nutritional intervention was higher than 80%, which may explain the better results than in other studies. For ONS, earlier studies have shown adherence rates of only approximately 50% (15). In a similar trial, adherence was 38% in the ONS group and 50% in the matched placebo group(15). Low adherence rates have also been reported for vitamin D supplementation. According to a meta-analysis, 21 of 29 trials had an adherence rate of calcium (and vitamin D) supplementation of less than 80%(8).

In contrast to most other studies, a dietitian counselled patients in the present study every other week (six times during the study period). The excellent adherence may be attributed to this counselling. This is supported by a recent study that also showed greater energy intake in the group that received counselling(37).

The study population was heterogeneous and differed in medical diagnosis, nutritional status, age, and health status. To increase homogeneity, patients from only two wards were included: internal medicine and traumatology/vascular surgery, representing the specialties general internal medicine, rheumatology, gastroenterology, dermatology,

nephrology, orthopaedics, traumatology, and vascular surgery. This population was carefully chosen and excluded patients undergoing major surgery.

This study has certain limitations. First, it was not blinded. Patients and investigators were aware of group assignment. Blinding the researcher during the analyses partially adjusted for this limitation, but socially desirable answers of patients could have biased the results. Therefore, a double-blind controlled design would have been preferable.
Second, a 2-week dietary history was used to assess patients' nutritional intake. The method of collection of nutrition data was not optimal, but it was the best available method considering the health status of the patients. Twenty-four-hour recall was not considered appropriate because most patients were very ill the day prior to hospital admission, so this would not give an accurate impression of usual intake. In addition, performing 24-hour recall would be too much an effort for this ill, frail population.
Finally, loss to follow-up was 30% because of mortality and withdrawal. These data could have biased the results. Fifty-three percent of these patients died or withdrew within the first 6 weeks. For these patients, no falls data were available. The fall incidence in patients who completed the first 6 weeks of the study and subsequently dropped out was not different from the incidence in patients who completed the whole study.

Conclusion

In summary, significantly fewer falls were seen in malnourished elderly patients receiving short-term nutritional intervention consisting of the combination of oral nutritional supplements, calcium and vitamin D, and dietetic counselling. This is one of the first studies showing these effects in such a short period and in a sample consisting of exclusively malnourished patients. It would be of interest to study the cost effectiveness of this intervention in the future.

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CHAPTER 6

Effects of nutritional intervention on immune markers in malnourished elderly

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Abstract

Background

Both malnutrition and advanced age are known to negatively impact the immune system.

The aim of this exploratory randomized controlled trial was to study the effects of a composed nutritional intervention on immune markers, endocrine markers and a selection of micronutrients in malnourished ill elderly patients.

Methods

Malnourished elderly patients (> 60 yrs) newly admitted to the departments of general internal medicine of a university medical center were randomised to receive either usual care plus a multi-component nutritional intervention (energy and protein enriched diet, comprising oral nutritional supplements, calcium-vitamin D supplement, telephone counselling by a dietitian) for three months post-discharge or usual care alone.

Immune markers (interleukins, complement, C-reactive protein, albumin, TNF-α), endocrine markers (growth factors) and micronutrients (iron, ferritin, vitamin A, E and D), were measured at baseline and three months following hospital discharge.

Results

In total 210 patients were included in this study, 105 in each group. For 89 patients (46 patients in the intervention group and 43 in the control group) both baseline and final measurement of immune markers, endocrine markers and micronutrients were available. This selection of patients appeared to be in a better health status compared to the total group. At baseline, most of the analysed immune markers, endocrine markers and micronutrients showed values within the normal range, with no statistically significant differences between intervention group and control group. Most immune markers, endocrine markers and micronutrients tend to improved over time, without statistically significant differences between groups, except for vitamin D (p=0.008), confirming the supplementation of vitamin D in the intervention group.

Conclusion

A three months nutritional intervention in malnourished ill elderly patients had no measurable additional influence on measured immune markers, endocrine markers and selected micronutrients. The improved outcomes were presumably caused by patients' improved health status during time.

Background

Malnutrition is of major concern in elderly hospitalized patients as it negatively impacts patients' health and as a consequence has a negative impact on clinical outcome (1;2). A recent nutritional intervention study (three months of oral nutritional supplements (ONS), additional calcium/vitamin D supplementation and dietetic counselling) showed weight gain and a decrease in functional impairment and falls in malnourished ill elderly patients (3;4). These effects could be explained by effects of energy and protein, leading to a positive balance between protein synthesis and protein breakdown(5) and/or vitamin D supplementation, leading to improvement of muscle strength and function(6). However, also restoration of the impaired immune system could possibly have affected the recovery of the supplemented group.

Both malnutrition and advanced age are known to negatively impact the immune system. Malnutrition per se affects nearly all aspects of the immune defence system, but especially impairs cell mediated immunity and resistance to infection(7).

In the elderly, many alterations of both innate and acquired immunity have been described. Although the emphasis of most research on immunosenescence has been on T cells, there is an increasing insight that the subtle changes seen in parameters of innate immunity, including the acquisition of some characteristics of innate immunity by T cells themselves(8-10), may have more influence on immunity than so far assumed(11-13).

Adequate nutrition is believed to play a role in the maintenance and restoration of impaired immune-competence, even in old age(14-16). Not only an adequate intake of energy and protein play an important role. Also, the correction of certain nutritional deficiencies has been demonstrated to improve the host's immunity, which warrants a place for these nutrients in an adequate diet. However, the optimal intake for a variety of micronutrients, to improve host's immunity, has not been established. To obtain an idea of the possible changes in the immune system in the period recovering from disease and malnutrition, a broad range of (surrogate) immune markers (interleukins, complement, C-reactive protein, albumin, TNF-α), endocrine markers (growth factors), and micronutrients (iron, ferritin, vitamins) will be assessed, to explore if these different compartments may explain the enhanced recovery of a malnourished ill elderly population following nutritional intervention.

In addition, data on antibiotic treatment will be collected, as patients with a slower recovery of their immune system are expected to be more susceptible to (recurrent) infections, and would thus require more antibiotic prescriptions.

Methods

Design

The current study is an exploratory sub-analysis of a parent study; the study design and primary results have been reported elsewhere(3;4;17). The parent study was a randomized controlled trial, comparing usual care plus oral nutritional supplements (ONS), calcium/vitamin D supplementation and dietetic counselling versus usual nutritional care alone in malnourished ill elderly patients, from hospital admission up until three months following discharge(17). In short, patients receiving the nutritional intervention improved in body weight and function(3), and fell less often(4) than those who did not receive the intervention. The current sub-analysis focuses on immune markers, endocrine markers and micronutrients. The study designs are in accordance with the Declaration of Helsinki and were approved by the Medical Ethics Committee (METC) of the VU University Medical Center, Amsterdam.

Patients

All elderly patients (≥ 60 years of age), newly admitted (expected length of hospital stay > 2 days) to the departments of general internal medicine, rheumatology, gastroenterology, dermatology, nephrology, orthopaedics, traumatology and vascular surgery of the VU University Medical Center were screened for malnutrition.

Patients were eligible for the study if they were identified to be malnourished according to the following criteria:

- Body Mass Index (BMI in kg/m^2) ≤ 20 and/or
- ≥ 5% unintentional weight loss (self-reported) in the previous month and/or
- ≥ 10% unintentional weight loss (self-reported) in the previous six months.

Details of the study design have been described extensively elsewhere(17). In short: a computerized random number generator was used to assign patients in blocks of ten to either the control group or the intervention group. Patients allocated to the control group received usual care, i.e. they were given nutritional support only on prescription from their treating physician. Generally, they did not receive post-discharge nutritional support on a standard basis.

Patients allocated to the intervention group received standardized nutritional support from hospitalization up until three months following discharge:

- Energy and protein enriched diet (only during the in-hospital period). Compared with the regular hospital menu, this diet provided an extra intake of about 750 kcal and 30 g protein per day.
- Two additional servings per day of an oral nutritional supplement (ONS; Nutridrink®, Nutricia N.V., Zoetermeer, The Netherlands) were offered. This was intended to provide per day an additional 600 kcal, 24 g protein, 176 IU vitamin D3, 364 mg calcium, 492 µg-RE vitamin A, 7.6 mg α-TE vitamin E and 9.6 mg iron, next to other macro- and micronutrients. Two bottles/day provide 40% of the recommended daily allowances of macro- and micronutrients) during the entire study period.
- 400 IU vitamin D3 and 500 mg calcium per day, during the entire study period. In The Netherlands vitamin D is usually given as a combined calcium/vitamin D supplement (Calci-Chew D3®, Nycomed bv, Hoofddorp, The Netherlands,).
- Telephone counselling by a dietitian was conducted every second week following hospital discharge (six sessions in total). The goal of counselling was to encourage adherence to the prescribed supplements.

The intake of all the prescribed supplements, after discharge from hospital, provides an additional 600 kcal, 24 g protein, 576 IU vitamin D3, 864 mg calcium, 492 µg-RE vitamin A, 7.6 mg α-TE vitamin E and 9.6 mg iron per day.

Outcome parameters

Immune markers, endocrine markers and micronutrients

Limited production and/or diminished functional capacity of all cellular components of the immune system have been reported, both in malnutrition and in old age. To understand the possible changes in the immune system in the period recovering from disease and malnutrition, several aspects of the immune system, endocrine system and micronutrients will be studied:

- inflammation; to study recovery from disease (C-reactive Protein, albumin)
- (pro)inflammatory cytokines which are pivotal to the inflammation that is associated with malnutrition (IL-1β, IL-2, IL-6, IL-8, IL-12, IL-17A, IL-22, IFN-γ, TNF-α)
- anti-inflammatory cytokines which inhibit production of inflammatory cytokines (IL-4, IL-10)
- endocrine changes; they occur during the systemic inflammatory response (IGF-1)
- complement components; the availability is compromised during malnutrition (C3 and C3d)

- cytolytic activity of cytotoxic T-cells/NK cells (granzyme B)
- micronutrients; they are supportive to the immune system and frequently deficient during malnutrition. Due to the limited amount of samples and decisions made in collection and storage, only iron, ferritin, 25-OH vitamin D, vitamin A and vitamin E were measured.

From each patient two tubes of blood were collected at both baseline and three months following discharge. The blood was centrifuged to remove cellular components and the serum left was frozen until analysis.
Details on storage, laboratory and measurements of the different immune markers, endocrine markers and micronutrients are presented in Table 1. Both samples from each patient were analyzed together in one run in order to minimize variation within patients.

Antibiotics
Data on antibiotic treatment was collected starting from one week following hospital discharge. Patients with a slower recovery of their immune system were expected to be more susceptible to (recurrent) infections, and would thus require more antibiotic prescriptions. Therefore, data on number of antibiotic prescriptions, duration (days), generic name, way of dispense (oral or intravenous) and dosage were collected.
Antibiotic use during hospitalization was excluded from the analyses because infection (requiring antibiotics) was the primary reason for admission to hospital in the majority of patients.

Table 1: Details on detection method, sample, storage and laboratory of immune markers, endocrine markers and micronutrients measured

Parameter	Detection method	Sample	Storage	Details
Complement C3 in µg/ml	Assessed by radial immunodiffusion using mono specific polyclonal rabbit antisera	Serum	–80°C	[3]
Complement C3d in µg/ml	A supernatant was assessed by rocket electrophoresis. The antiserum used was a monospecific polyclonal goat antibody against C3d, prepared by immunization with purified C3d. A standard with known contents of C3d was included in each assay.	Serum	–80°C	[3]
Ratio C3d/C3 in µg/ml	Ratio = C3d/C3	Serum	–80°C	[3]
IL-2R in pg/ml	ELISAs* were performed according to the manufacturers instructions of Diaclone	Serum	–80°C	[2]
IL-12 in pg/ml	ELISAs* were performed according to the manufacturers instructions of Biolegend	Serum	–80°C	[2]
IL-17A in pg/ml	ELISAs were performed according to the manufacturers instructions of Diaclone	Serum	–80°C	[2]
IL-22 in pg/ml	ELISAs were performed according to the manufacturers instructions of Biolegend	Serum	–80°C	[2]
IL-1β in pg/ml	ELISAs* were performed according to the manufacturers instructions of Sanquin	Serum	–80°C	[2]
IL-4 in pg/ml	ELISAs* were performed according to the manufacturers instructions of Sanquin	Serum	–80°C	[2]
IL-6 in pg/ml	ELISAs* were performed according to the manufacturers instructions of Sanquin	Serum	–80°C	[2]
IL-8 in pg/ml	ELISAs* were performed according to the manufacturers instructions of Sanquin	Serum	–80°C	[2]
IL-10 in pg/ml	ELISAs* were performed according to the manufacturers instructions of Sanquin	Serum	–80°C	[2]
TNF-α in pg/ml	ELISAs* were performed according to the manufacturers instructions of Sanquin	Serum	–80°C	[2]
Albumin in g/L	Chemically determined on a Modular P analyzer (ACN 760, 11815148 216, Roche Diagnostics, Almere, The Netherlands)(27)	Serum	–20°C	[1]
Iron in µmol/L	Analyzed by a colorimetric assay on a Modular P analyser (Roche diagnostics, Mannheim, Germany)	Serum	–20°C	[1]

Table 1: (continued)

Parameter	Detection method	Sample	Storage	Details
Ferritin in µg/L	Analyzed by an electro chemiluminescence immunoassay on a Modular E analyser (Roche diagnostics, Mannheim, Germany)	Serum	–20°C	[1]
Total iron binding capacity (TYBC) in µmol/L	Calculated by transferrine (g/L) * 25 = TYBC (µmol/L)	Serum	–20°C	[1]
Iron saturation in %	Iron saturation was calculated by 100 * [Iron (µmol/L)/ TYBC (µmol/L)] = % transferrin saturation	Serum	–20°C	[1]
IGF-1 in nmol/L	Determined by an enzyme-labelled chemiluminescent immunometric assay on a Immulite 2500 (Siemens medical solutions Diagnostic, USA)	Serum	–80°C	[2]
CRP in mg/L	Analyzed by an automated latex-enhanced immunoturbidimetric assay on a Modular P analyser(28).	Plasma	–20°C	[1]
25-hydroxy vitamin D in nmol/L	Analyzed by radioimmunoassay (Diasorin, Stillwater, MN, USA)	Serum	–20°C	[1]
Vitamin A (retinol) in µmol/L	Determined by a modification of a published procedure(29). Briefly, after addition of the internal standard tocol, the plasma samples were de-proteinized with ethanol and extracted with *n*-hexane. After evaporation of the extract, the residue was dissolved in ethanol and analyzed by isocratic reversed-phase high-performance liquid chromatography. Detection was performed by UV absorption at wavelengths of 325 nm.	Plasma	–80°C	[4]
Vitamin E (α-tocopherol) in µmol/L	Determined by a modification of a published procedure(29). Briefly, after addition of the internal standard tocol, the plasma samples were deproteinized with ethanol and extracted with *n*-hexane. After evaporation of the extract, the residue was dissolved in ethanol and analyzed by isocratic reversed-phase high-performance liquid chromatography. Detection was performed by UV absorption at wavelengths of 280 nm.	Plasma	–80°C	[4]

** ELISAs; Enzyme Linked Immuno-Sorbent Assay*

[1] Endocrine Laboratory of the VU University Medical Center

[2] Medical Immunology Laboratory of the VU University Medical Center

[3] Medical Immunology Laboratory of the Leiden University Medical Center

*[4] Metabolic Laboratory of the VU University Medical Center; s*era were re-frozen at –80°C until analysis

Statistical methods

Mean (SD) or median (IQR) levels at baseline and at three months following discharge were calculated (for normally and non-normally distributed parameters respectively). Differences between the groups were tested by independent t-tests (normally distributed parameters or Mann-Whitney U tests (non-normally distributed parameters). Differences in dichotomous variables were tested by chi-square tests. Delta's express differences between baseline and final measurement.

Interleukin levels were often below detection limit (absolute value zero), resulting in zero or negative delta's. Therefore the delta's for interleukins were categorized into three groups (<0, 0 and >0) and tested by chi-square.

In addition, sub-analyses by paired t-tests were performed excluding patients with baseline interleukin levels below the detection limit (i.e. excluding patients for whom interleukin levels were already optimal).

Sub-analyses were performed to study if age (≤ versus > the median age of 75 y) and degree of malnutrition (severe malnutrition: BMI < 18.5 and/or > 5% unintentional weight loss in the previous months plus > 10% unintentional weight loss in the previous six months versus less severe malnutrition: all other) influenced the relation with immune function. The statistical analyses were restricted to patients with complete follow-up. Statistical significance was defined as $p \leq 0.05$. Statistical analyses were performed using the SPSS-system for Windows, version 17.0 (SPSS, Chicago, IL, USA).

Results

In total 210 patients were included in this study, 105 in each group. Sixty patients were lost to follow-up, due to death (n=25) or withdrawal (n=35). Another thirty patients were too ill to visit the outpatient clinic of the hospital for the second blood sample collection and in 31 patients logistical problems were responsible for the failure of the second measurement. For 89 patients (46 patients in the intervention group and 43 patients in the control group) both baseline and final measurement were available.

Group selection

At baseline, statistically significant differences were observed between patients with both measurements available (n=89) versus patients with only a baseline measurement available (n=192) for age (included patients were younger, p=<0.000), gender (included patients were more often male, p=0.001), body weight (included patients had a higher body weight, p=0.001), iron (included patients had higher iron levels, p=0.003), iron saturation (included patients had higher iron saturation percentages, p=0.004) and IL-12 (included patients had higher IL-12 levels, p=0.042).

Remarkably, in this subgroup of 89 patients, no statistically significant improvement between groups for functional limitations p=0.538, 95% CI -0.747 to 0.393), number of falls (p=0.108, 95% CI -0.384 to 3.811) and body weight (p=0.378, 95% CI -0.341 to 0.131) could be demonstrated following three months of nutritional intervention, which is in contrast to previous published results within the total group of 210 patients(3).

Baseline and clinical characteristics

For patients with both measurements available, there were at baseline, no statistically significant differences in baseline and clinical characteristics between groups (Table 2).
With the used assay it was not possible to detect granzyme B in any of the patients either at baseline or three months following discharge.
A pilot study of 50 patients demonstrated that IFN-γ levels were below detection limits in 46 patients at both hospital admission and three months following discharge. Decision was made not to analyze IFN-γ in other patients.

Antibiotics

Thirty-four patients (17%, 14 patients in the intervention group and 20 patients in the control group) used antibiotics following hospital discharge. For 10 patients (5%, 6 in the intervention group and 4 in the control group) data on use of antibiotics were missing. There were no statistically significant differences between the intervention group and control group regarding the number of patients with antibiotic prescriptions (p=0.287), the total number of antibiotic prescriptions (p=0.286) and the duration of use (p=0.226).

Immune markers and endocrine markers

At baseline, immune markers and endocrine markers were within the normal range of reference values for the majority of patients, with no statistically significant differences between the intervention and control group (Table 3). CRP (inflammatory marker) was increased at baseline and albumin (negative phase protein) was decreased, however this was expected and in conformity with the acute hospital admission. Most interleukin levels were below detection limits. Therefore, sub-analyses were performed in which levels were split up in two groups: under or above the median. No statistically significant differences between groups could be demonstrated.

Table 2: Baseline and clinical characteristics between the intervention group versus the control group

Characteristics	Intervention group (n=46)	Control group (n=43)	*p*-value
Gender – number of females (%)	17 (37.0)	20 (46.5)	0.407 [b]
Age in yr – mean (±SD)	71.6 (8.4)	71.3 (7.8)	0.733 [a]
Home situation – no. (%)			0.533 [b]
Living alone	19 (41.3)	21 (48.8)	
Living with partner / family	27 (58.7)	22 (51.2)	
Consulting dietitian pre-admission – no. (%)	15 (32.6)	7 (16.3)	0.103 [b]
Use of supplemental drinks pre-admission – no. (%)	11 (23.9)	10 (23.3)	0.896 [b]
Body weight – mean (±SD)	65.5 (14.6)	60.8 (13.4)	0.114 [a]
Men	69.1 (15.6)	66.0 (9.9)	
Women	59.4 (10.3)	54.9 (10.2)	
Body Mass Index in categories – no. (%)			0.187 [b]
BMI ≤ 20	22 (47.8)	21 (48.8)	
BMI 20 – 25	14 (30.4)	18 (41.9)	
BMI ≥ 25	10 (21.7)	4 (9.3)	
Weight change last month – % (±SD)	-4.9 (5.4)	-3.5 (7.7)	0.343 [a]
Weight change last six months – % (±SD)	-9.7 (7.3)	-8.1 (7.7)	0.359 [a]
Primary medical diagnosis – no. (%)			0.396 [b]
Acute	25 (54.3)	20 (46.5)	
Chronic	21 (45.7)	23 (53.5)	
Primary medical diagnosis in categories – no. (%)			0.339 [b]
Acute infections	12 (26.1)	4 (9.3)	
Vascular disease	7 (15.2)	9 (20.9)	
Kidney insufficiency	6 (13.0)	5 (11.6)	
Fractures, orthopaedic disorders	3 (6.5)	6 (14.0)	
Malignant neoplasm	3 (6.5)	6 (14.0)	
Chronic bowel disease	7 (15.2)	7 (16.3)	
Diabetes Mellitus, heart failure and other	4 (8.7)	2 (2.7)	
Bleeding in gastrointestinal tract	3 (6.5)	1 (2.3)	
Liver, gall and pancreas insufficiency	1 (2.2)	3 (7.0)	

[a] *t-test*

[b] *Chi² test*

Table 3: Differences in immune markers, endocrine markers and micronutrients between hospital admission and three months after discharge in patients in the intervention group versus patients in the control group

Parameter	Reference value*	Intervention group		Control group		Difference in Δ (95% CI)
		Baseline (n=46)	Final (n=46)	Baseline (n=43)	Final (n=43)	
Complement C3 †	470-800 µg/ml	683.6 (149.4)	661.8 (111.8)	663.9 (150.0)	670.5 (112.6)	0.463 (-37.0 to 80.7)[a]
Complement C3d †	0-29 µg/ml	16.5 (7.4)	11.1 (4.5)	17.4 (9.3)	13.1 (7.7)	0.530 (-2.4 to 4.7) [a]
Ratio complement C3d/C3 †	-	0.03 (0.02)	0.02 (0.01)	0.03 (0.02)	0.02 (0.01)	0.783 (-0.01 to 0.01) [a]
CRP ‡	<8.0 mg/L	37.5 (3.0-110.5)	5.0 (2.5-17.3)	28.5 (8.0-69.0)	2.8 (2.5-19.3)	0.162[c]
IL-12 ‡	< 2 pg/ml	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.054[b]
IL-1β ‡	< 5 pg/ml	0.02 (0.0-0.6)	0.01 (0.0-1.4)	0.02 (0.0-1.2)	0.01 (0.0-1.5)	0.567[b]
TNF-α †	< 10 pg/ml	25.1 (103.1)	19.2 (63.0)	2.5 (9.0)	8.4 (43.2)	0.662[b]
IL-2R ‡	< 6400 pg/ml	4945 (3231-9860)	4190 (2291-7660)	4177 (2791-6392)	3234 (3232-6284)	0.661[b]
IL-17A ‡	< 3 pg/ml	0.0 (0.0-29.0)	0.0 (0.0-29.8)	0.0 (0.0-35.0)	0.0 (0.0-22.5)	0.334[b]
IL-22 ‡	< 10 pg/ml	181.6 (0.0-340.3)	0.0 (0.0-229.5)	161.6 (0.0-251.7)	0.0 (0.0-231.2)	0.663[b]
IL-6 ‡	< 10 pg/ml	5.3 (0.0-18.9)	0.0 (0.0-0.0)	3.2 (0.0-13.5)	0.0 (0.0-0.0)	0.889[b]
IL-8 ‡	< 10 pg/ml	22.4 (16.1-43.1)	18.9 (11.2-22.9)	22.0 (10.7-47.3)	18.0 (10.6-23.8)	0.639[b]
IL-4 ‡	< 1 pg/ml	0.0 (0.0-9.1)	1.9 (0.0-7.2)	0.0 (0.0-5.9)	0.0 (0.0-2.9)	0.729[b]
IL-10 ‡	< 5 pg/ml	0.0 (0.0-1.3)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.834[b]
Albumin †	35-52 g/L	30.9 (6.9)	38.7 (7.3)	31.4 (5.7)	38.9 (6.8)	0.968 (-3.3 to 3.4)[a]
Iron ‡	11-32 µmol/L	9.0 (5.0-16.0)	11.0 (9.0-16.0)	7.0 (4.3-12.8)	12.0 (8.3-16.0)	0.508[c]
Ferritin ‡	20-375 µg/L	325.0 (153-586)	107.0 (56-321)	290.0 (138-681)	169 (55-391)	0.929[c]
Total iron binding capacity ‡	45-90 µmol/L	47.0 (35.0-56.0)	61.0 (52.0-70.0)	46.0 (36.0-58.0)	57.0 (50.0-68.0)	0.243[c]
Iron saturation ‡	12–50%	17.0 (12.0-34.0)	20.0 (14.0-26.0)	14.0 (10.0-27.8)	20.5 (13.0-28.0)	0.211[c]
IGF-1 †	6.8-23 nmol/L	11.9 (6.0)	16.4 (8.2)	11.8 (6.9)	15.9 (7.5)	0.675 (-4.3 to 2.8)[a]
25-hydroxy vitamin D †	>50 nmol/L	41.7 (20.2)	66.0 (25.0)	43.6 (22.2)	56.4 (25.5)	**0.008 (2.9 to 19.0)**[a]
Vitamin A †	1.2-3.0 µmol/L	2.0 (1.0)	2.9 (1.1)	2.0 (1.0)	2.9 (1.2)	0.909 (-0.5 to 0.4)[a]
Vitamin E †	20-39 µmol/L	25.1 (10.1)	30.3 (10.1)	27.5 (11.7)	34.3 (11.5)	0.630 (-2.7 to 4.5)[a]

† Mean (± standard deviation)
‡ Median (inter quartile range 0.25-0.75)
** Reference values according to the VUmc, Amsterdam, The Netherlands*

[a] *t-test*
[b] *Chi² test*
[c] *Mann-Whitney U test*

Table 3 also shows the differences between hospital admission and three months following discharge. The deltas between the two measurements were calculated and the statistical differences between the deltas are listed in the final column.
Three months following discharge, there were no statistically significant differences between groups for immune markers and endocrine markers.

Micronutrients
At baseline, micronutrient levels were within the normal range of reference values for the majority of patients, except for vitamin D (deficient levels) and iron and total iron binding capacity (decreased levels, matching with the observed acute phase response). No statistically significant differences between the intervention and control group were observed at baseline (Table 3).
Three months following discharge, there were no statistically significant differences between groups for vitamin A, E and iron, whereby total iron binding capacity had increased to normal values. However, a statistically significant increase in vitamin D level was demonstrated in favour of the patients allocated to the intervention group (p=0.008), which was expected on forehand because of the supplementation of vitamin D to these patients.

Influence of age and degree of malnutrition
Sub-analyses were performed across groups, to analyze whether age and degree of malnutrition mattered. Literature describes that older age and more severe malnutrition affect the immune system most. Therefore, analyses have been performed to study whether differences could be demonstrated between younger old patients (≤ 75 year) and older old (> 75 year) patients. The same analyses have been performed for the most severely malnourished versus the less severely malnourished patients (see methods).
Independent of group assignment, and independent of baseline levels, statistically significant differences for vitamin D were demonstrated. Older old patients improved their vitamin D levels more than younger old patients (p=0.010); the severely malnourished patients improved less than the less severely malnourished patients (p=0.009).
For all other micronutrients, endocrine markers and immune markers analysed, no statistically significant differences could be demonstrated.

Discussion

Nutrient deficiencies can cause immuno-suppression and dysregulation of immune responses. From the immune markers, endocrine markers and micronutrients measured in this study conclusion can be made that all malnourished ill elderly patients improved during the three months following hospital discharge; inflammation decreased, most interleukins decreased and vitamin levels increased. In literature described associations between malnutrition, illness and immune function could be not demonstrated in the present study.

At baseline, immune markers, endocrine markers and micronutrients were predominantly within the normal range of references values. Several studies have described associations between malnutrition, old age and impaired immune function(1;18). This exploratory study does not confirm these data.
Although the immune markers, endocrine markers and micronutrient levels improved over time, the nutritional intervention, in this malnourished ill elderly patient group had no additional influence on (the restoration of) these markers. In this study no increase in fat mass after the nutritional intervention, could be observed(3). The possible change in immune markers associated with increased fat mass (CRP, IL-6, TNF-α and IGF-1(19)) was not observed either. Hypothesis can be made that the improved outcomes were most likely due to general improved health status over time in both groups.

Complete blood samples at both time points were available for only 89 out of 210 patients. We do not expect that an increased sample size would have altered the results. Most patients showed immune markers and micronutrient levels already within the normal limits at baseline, indicating that there was marginal opportunity for improvement. The relatively good starting point of patients is most likely the reason for not seeing marked changes over time.

Use of antibiotics during the study period may have influenced infection related cytokine (e.g. IL-6 and IL-8) release. Treatment with antibiotics was assessed between the baseline and final measurements. Therefore it was not possible to evaluate the influence of antibiotics on serum cytokine levels. However, antibiotics usage did not differ between the intervention and control group and is therefore not likely to have influenced the outcome of the analysis. In a post-hoc analysis, no statistically significant differences between patients with a decrease in cytokine and CRP levels and the usage of antibiotics could be demonstrated.

This exploratory study was designed to study the effects of 'regular' macronutrients and micronutrients only. It is possible that these malnourished ill elderly patients may have had more specific needs. Future studies could focus on improvement of immune markers by specific immunonutrients known to have an immunomodulatory effect e.g. glutamine, arginine, nucleotides, poly unsaturated fatty acids, probiotics or prebiotics such as fructooligosaccharides or galactooligosaccharides, or a higher dosage of micronutrients (e.g. the vitamins A, B6, B12, C, D E, and the trace elements folic acid, iron, cupper and selenium)(16;20-22).

In animal studies, burns, injury and infection have been associated with depletion of antioxidant vitamins and trace elements; however, data on humans are only limited available. In this small exploratory study, all studied micronutrients (except vitamin D) were predominantly within normal ranges at the baseline measurement, which was unexpected because of patients' poor nutritional status. Levels increased over time (although not statistically significant), however, not more in the patients who received the nutritional intervention than in controls. The two bottles of oral nutritional supplements accounted for 40% of the recommended daily allowances of micronutrients. Therefore, it was surprising that there was no improvement in serum levels of the measured micronutrients. Although, on the other hand, levels are not representative of a patient's actual micronutrient status due to the negative acute phase response(23) or because the actual body provision is stored in the liver (vitamin A en E).
At baseline, vitamin D levels were deficient. This is in line with previous findings by other studies and a Cochrane review on interventions for preventing falls in elderly people(24;25) In both groups, serum vitamin D levels increased, however more in the intervention group than in the control group, most likely due to the extra supplementation to intervention patients(4). The supplied dosage of vitamin D (176 IU by ONS and 400 IU by calcium-vitamin D3 supplementation) was lower than the most recent advice by the Health Council of The Netherlands for elderly people since 2008: 800 IU/day(26). Remarkably, vitamin D levels increased more in older old patients than in younger old ones; this was also the case for less severely malnourished patients, irrespective of group assignment and independent of baseline levels. We have no clear explanation for these results.
Although the emphasis of most research on immunosenescence has been on T cells, there is an increasing insight that the subtle changes seen in parameters of innate immunity, including the acquisition of some characteristics of innate immunity by T cells themselves (8;9), may have more influence on immunity than so far assumed. Both malnutrition and advanced age are known to negatively impact the immune system. Malnutrition per se affects nearly all aspects of the immune defence system, but

especially impairs cell mediated immunity and resistance to infection(7). In the elderly, many alterations of both innate and acquired immunity have been described(14;15). In this study, the old and more malnourished subpopulations did not differ in immune markers, endocrine markers and micronutrients from their younger and less malnourished counterparts, except for vitamin D.
Immunosenescence is accompanied with low grade inflammation. In this trial the levels of CRP and IL-6 returned to normal values and were not in line with reports on increased CRP and IL-6 levels of low grade inflammation in elderly(8;13).

Approximately 50% missing values on immune markers, endocrine markers and micronutrients were faced during the final measurement. The patients with both (baseline and final) measurements available were younger, had higher body weight and more biochemical parameters that were representative according to the normal values. In addition, the majority of included patients had interleukin levels below detection limits, indicating non-disturbed cytokine levels. Furthermore, earlier demonstrated statistically significant differences in functional limitations, fall incidents and body weight could not be demonstrated in this subgroup of patients with immune markers, endocrine markers and micronutrients available at both measurements.
Therefore, hypothesis is made that the most severely ill patients were excluded from analyses in this exploratory study. Differences were observed between patients with both measurements available (n=89) versus patients with only a baseline measurement available (n=192). Included patients were younger, more often male, had a higher body weight, higher iron levels, higher iron saturation percentages and higher IL-12 levels.
The exclusion of the most severely ill patients can possibly explain the fact that no differences in immune markers, endocrine markers and micronutrients (except for vitamin D) between groups could be demonstrated. No statistical significant differences were shown in antibiotic usage between included and excluded patients (data not shown). In addition, baseline levels of immune markers, endocrine markers and micronutrients were mostly within the normal range of references values.

Conclusion

Although the nutritional modulation of immune function has attracted much attention recently, predominantly by the use of immunemodulating agents, the presumed immunestimulating role of 'regular' macronutrients and micronutrients, except for vitamin D and E, has received only little attention. This exploratory study on three months nutritional intervention, in a malnourished ill elderly patient group could not demonstrate statistically significant improvement of immune markers, endocrine

markers and selected micronutrients. This may be caused by the unintentional selection of healthiest patients, the variety of underlying diseases in patients, the supplied nutritional intervention, the used tests for measuring immune markers and/or the choice that was made to only measure at baseline and three months following hospital discharge.

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CHAPTER 7

Resting energy expenditure in malnourished elderly patients at hospital admission and three months following discharge: predictive equations versus measurements

In press:
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Resting energy expenditure in malnourished elderly patients at hospital admission and three months following discharge: predictive equations versus measurements
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Abstract

Background

Predicting resting energy expenditure (REE) in malnourished hospitalized elderly patients is important for establishing optimal goals for nutritional intake. Measuring REE by indirect calorimetry is hardly feasible in most clinical settings.

The objective of this study was to study the most accurate and precise REE predictive equation for malnourished elderly patients at hospital admission and again three months following discharge.

Methods

Twenty-three equations based on weight, height, gender, age, fat free mass (FFM) and/or fat mass (FM) and eleven fixed factors of kcal/kg were compared to measured REE. REE was measured by indirect calorimetry. Accuracy of REE equations was evaluated by the percentage patients predicted within 10% of REE measured, the mean percentage difference between predicted and measured values (bias) and the Root Mean Squared prediction Error (RMSE).

Results

REE was measured in 194 patients at hospital admission (mean 1473 kcal/d) and again three months following hospital discharge in 107 patients (mean 1448 kcal/d). The best equations predicted 40% accuracy at hospital admission (Lazzer, FAO/WHO and Owen) and 63% three months following discharge (FAO/WHO). Equations combined with FFM, height or illness factor predicted slightly better. Fixed factors produce large RMSE's. All predictive equations showed proportional bias, with overestimation of low REE values and underestimation of high REE values. Correction by regression analysis did not improve results.

Conclusion

The REE predictive equations are not adequate to predict REE in malnourished hospitalized elderly patients. There is an urgent need for either a new accurate REE predictive equation, or accurate easy-to-use equipment to measure REE in clinical practice.

Background

The number of people in Europe aged 65-79 years is expected to increase approximately 35% between 2010 and 2030(1). Elderly are especially vulnerable to malnutrition as they often have several co-morbidities that are chronic and progressive. Adverse effects of malnutrition vary from impaired wound healing and postoperative complications to mortality(2). Poor nutritional status has not only been associated with in-hospital adverse effects, but also with adverse effects both pre-admission and post-discharge. These effects include a trend for increased need for re-hospitalization, significantly higher total mortality, a higher general practitioner consultation rate, higher medication prescription rate, longer rehabilitation, an increased need for nursing home admission, increased likelihood of requiring home health care following discharge and early institutionalization(3;4). The prevalence of malnutrition in free-living elderly is 13-37%(5-8) and can increase up to 93%(9-12) in hospital admitted elderly.

Malnutrition is often reversible and can be treated by a dietitian, general practitioner or medical specialist. For establishing optimal goals for dietary intake it is important to predict resting energy expenditure (REE). This requires knowledge of individual energy requirements and relies on accurate methods of assessment. Energy expenditure can be measured by indirect calorimetry and provides an indication of patients' energy requirements(13). This method is hardly feasible in most clinical settings, due to time consuming measurements, lack of trained personnel and expensive equipment. In clinical practice, predictive equations to determine REE in malnourished elderly patients are used as an alternative to solve this problem.

REE predictive equations have generally been developed in healthy populations or in critically ill patients. Specific equations for predicting REE in malnourished hospitalized elderly patients are lacking. Earlier we showed that the percentage accurate predictions for inpatients (not elderly) was only about 40%(14). Melzer et al.(15) showed for healthy elderly (≥ 70 years) that the Harris-Benedict equation resulted in 72% accurate predictions, suggesting that being old per se is not limiting the accuracy. The existing REE predictive equations have not been tested in a mixed diagnosed group of malnourished hospitalized elderly patients.

The aim of this study was to find the most accurate and precise REE predictive equation. As part of evidence-based practise, the literature was systematically searched for REE predictive equations. Subsequently REE equations were compared with measured REE data from indirect calorimetry at hospital admission and again three months following discharge in malnourished elderly patients aged ≥ 60 years.

Methods

Patients

The patients were recruited between March 2006 and September 2009 from the clinical departments of Internal Medicine, Traumatology, Orthopaedics, and Vascular Surgery of the VU University Medical Center Amsterdam. Patients were admitted in acute (49%) or chronic condition (51%).

The inclusion criteria were 1) age ≥ 60 years and 2) malnourished, defined as a Body Mass Index (BMI in kg/m^2) ≤ 20 and/or ≥ 5% unintentional weight loss in the previous month and/or ≥ 10% unintentional weight loss in the previous six months. Patients were excluded from the study when they suffered from senile dementia, could not understand the Dutch language or were unable to or willing to give informed consent.

The study was approved by the Medical Ethics Committee of the VU University Medical Center Amsterdam(16).

Indirect calorimetry

Resting energy expenditure was measured twice; at baseline (within 3 days after admission to the hospital) and three months following hospital discharge (final). Measurements were standardized by internal guidelines(17).

The indirect calorimetry measurements were performed with a ventilated-hood system (Vmax Encore 29n; Viasys Health Care, Houten, The Netherlands). The patients were in supine position, awake, and had not been physically active for at least 30 minutes prior to the measurement. The measurements took 30 minutes and data from the first five minutes of the measurement were excluded. The steady state period during the measurement was with acceptable coefficient of variation of 10%. Measurements of patients with a respiratory quotient (RQ) of < 0.7 and > 1.0 were excluded.

The Vmax system was calibrated daily for flow and two different standard gases (one with 26% O_2 and 0% CO_2 and one with 16% O_2 and 4% CO_2) immediately prior to use and every five minutes during the measurement. Oxygen consumption and carbon dioxide production were measured, and energy expenditure was calculated by the Weir equation(18). Oxygen analyser sensitivity was checked yearly by the supplier.

Body composition

Body composition was assessed by bio-electrical impedance spectroscopy (multi-frequency ECF/ICF Bio Impedance Spectrum Analyzer, Hydra 4200, Xitron Technologies, San Diego, CA, USA) to determine fat free mass and fat mass. Fat free mass and fat mass were calculated based on the Hanai mixture equation(19).

Body weight was measured, with patients wearing light indoor clothes and no shoes, on a calibrated electronic scale (Prior MD-1512), with an accuracy of 0.1 kilogram. A

correction factor for clothes was made by deducting weight with 2.0 kg for men and 1.3 kg for women(20). As measurement of height is often not feasible in this ill and frail elderly population, data on height were self-reported. BMI was calculated as actual weight in kilograms divided by the square of height in meters.

REE predictive equations

PubMed was used for a systematic search for publications on Mesh-derived keys 'Energy metabolism', 'Basal metabolism', 'Indirect calorimetry' and additional terms ('predict*', 'estimat*', 'equation', and 'formula') and age terms ('old(er)', 'elder(ly)', 'age 65 years') in every possible combination. Applied limitations were 'English language' and 'humans'. More references were obtained by screening publications cited looking back and forward.

Due to the limitation of age, only two references were found (Fredrix et al.(21) and Luhrmann et al.(22)). Therefore, we decided to further ignore the age limitation.

Inclusion criteria were as follows: equations based on body weight, height, age, sex and/or fat free mass and fat mass. Equations were excluded when they were based on children, obese persons, critically ill patients in which ventilation parameters were included, specific ethnic groups, small sample size ($n < 40$), complex measurements of body composition as variable, biochemical parameters, indirect calorimetry measurements with poor equipment and total energy expenditure.

From each included study the best performing equations based on the highest value for explained variance (R^2), were included. However, extra equations were included when based on weight and height (versus weight only) or FFM. In total, 23 equations were included in this study.

Because prediction equations do not include an illness factor, a range of illness factors(0-30%) that may improve percentage accurate prediction were added to the different equations.

For each patient, the REE was predicted by the selected equations in kcal/d and compared with measured REE. The actual body weight at the time of the indirect calorimetry measurement was used.

Fixed factors of kcal per kg

Besides existing predictive equations from the literature, we have calculated a range of 11 different fixed factors of kilocalories per kg body weight (15-40 kcal/kg body weight) to predict REE. For fixed factors, that provide total energy expenditure (TEE), predictions were divided by 1.3 to provide REE. From literature, an amount of 21-22 kcal/kg for REE that was suggested for use in the elderly(23;24), is comparable with 27.5 kcal/kg for TEE.

Statistics

Patient characteristics were analyzed by independent-samples *t* test. At individual level, prediction between 90-110% of measured REE was considered as accurate prediction. A prediction below 90% of REE measured was classified as under prediction and a prediction above 110% of REE measured was classified as over prediction(25;26).

The percentage of subjects that had an REE predicted within $\pm$10% of measured REE was considered a measure of accuracy(27). Bias, the mean percentage difference between REE predicted and REE measured was considered as a measure of accuracy on a group level. On forehand, we decided that the best equation had highest percentage accurate predictions and a percentage bias between -2.5 to +2.5. The root mean squared prediction error (RMSE in kcal/d) was used to indicate how well the model predicted, and is preferred over bias only(26;28). Bland-Altman plots were used to express the agreement between selected prediction equations and measured REE. R^2 is the proportion of variability in a data set that is accounted for by the statistical model. Since Bland-Altman plots showed a systematic association which caused overestimates at low REE and underestimates at high REE, regression analyses of REE predicted versus REE measured was used to adjust REE equations to this specific patient group. REE predicted values were re-calculated and checked for percentage accurate predictions, bias and RMSE.

Poor accuracy of predictions could have been caused by worse predictions in patients who did not have a follow-up measurement at three months following discharge (the most severely ill patients and the deceased). Therefore, statistics were also performed excluding patients without follow-up.

Data were analyzed using the SPSS-system for Windows, version 16.0 (SPSS, Chicago, IL, USA) and RMSE with Excel (Microsoft Office Excel 2003, Amsterdam, The Netherlands).

Results

A total of 210 malnourished hospitalized elderly patients were included in this study. Sixteen patients were excluded due to incomplete data on REE. Patient and clinical characteristics of 194 patients (104 women, 90 men) at hospital admission and 107 patients (47 women, 60 men) three months following hospital discharge are shown in Table 1.

Table 1: Patient and clinical characteristics at hospital admission (baseline; n=194, 104 females) and three months following hospital discharge (final; n=107, 47 females)

Characteristics	Total	Women	Men
Age (years)‡	74.3 (9.1)	75.9 (9.3)	72.5 (8.5)
Height (cm)‡	170.4 (7.9)	165.8 (6.0)	175.6 (6.5)
Body weight (kg)‡			
Baseline	60.1 (12.8)	54.6 (10.6)	66.5 (12.3)
Final	64.7 (13.3)	58.7 (9.5)	69.4 (14.0)
BMI (kg/m^2)‡			
Baseline	20.7 (4.0)	19.9 (3.8)	21.6 (3.9)
Final	21.8 (4.1)	21.1 (3.6)	22.4 (4.4)
BMI < 20 kg/m^2 (%)‡			
Baseline	54.9	64.4	44.0
Final	29.7	33.7	25.3
% weight change last month (kg) ‡			
Baseline	-4.5 (6.5)	-4.3 (6.7)	-4.7 (6.2)
Final	2.3 (4.7)	1.9 (5.0)	2.7 (4.4)
% weight change last 6 months (kg) ‡			
Baseline	-9.0 (7.4)	-9.2 (7.2)	-10.0 (7.6)
Final	-0.8 (9.2)	-1.4 (10.2)	-0.4 (8.3)
REE (kcal/d) ‡			
Baseline	1473 (311)	1331 (236)	1636 (307)
Final	1447 (291)	1280 (167)	1578 (301)
RQ‡			
Baseline	0.84 (0.08)	0.85 (0.10)	0.84 (0.07)
Final	0.90 (0.10)	0.89 (0.09)	0.90 (0.11)
Fat mass (%)†			
Baseline	22.3	23.3	21.3
Final	21.6	22.5	20.8
Fat mass (kg)†			
Baseline	14.4 (8.0)	13.8 (7.3)	15.1 (8.6)
Final	14.5 (6.9)	13.4 (6.5)	15.4 (6.5)
FFM (kg)†			
Baseline	47.6 (8.0)	42.8 (5.7)	52.3 (7.2)
Final	50.5 (9.6)	44.3 (5.4)	56.1 (9.2)

Mean ±SD, except for fat mass (%)

‡ Age, height, body weight, BMI, % weight change, REE and RQ: baseline n=194 (104 female), final measurement n=107 (47 female)

† Fat mass and FFM: baseline n=135 (67 female), final measurement n=89 (42 female)

At baseline, fifty-five percent of patients had a BMI below 20 kg/m^2 and 22% of patients below 18 kg/m^2. Seventeen percent of patients had > 10% weight loss over the last month and 49% of patient had > 10% weight loss over the last six months.
REE data are provided as kcal/d, percentage accurate predictions, percentage underprediction, percentage overprediction, percentage bias, RMSE, maximum underprediction, and maximum overprediction at hospital admission (Table 2) and three months following hospital discharge (Table 3).

Mean measured REE at hospital admission was 1473 kcal/d (SD 311) and 1448 kcal/d (SD 289) three months following hospital discharge (not statistically significant different (p=0.354)).
Mean body weight at hospital admission was 59.9 kg (SD 12.7) and 62.9 kg (SD 13.4) three months following discharge.
At hospital admission the equations of Lazzer, FAO/WHO-weight and height and Owen were the most accurate and precise, with for all three equations a 40% accuracy and -0.6%, -4.3%, and -5.1% bias, respectively. Only the equation of Lazzer fulfilled the pre-set criteria for accurate prediction.
Excluding patients without follow-up measurements of REE did not alter the results. The best prediction still predicted only 40% of these patients accurately (n=89).
Three months following hospital discharge, the equation of FAO/WHO-weight and height and Owen were the most accurate and precise and fulfilled the pre-set criteria for accurate prediction, with 63% and 60% accuracy with +1.2% and +0.4% bias, respectively.

The difference in percentage accurate prediction in weight-based equations versus FFM-based equations from the same reference is shown in Figure 1a.
Performance of FFM-based equations versus weight-based equation were inconsistent.
The difference in percentage accurate prediction of weight-based equations versus weight-height-based equations is shown in Figure 1b. Weight-height-based equations predicted slightly better.

Table 2: Evaluation of resting energy expenditure (REE) predictive equations in 194 hospitalized malnourished elderly patients based on bias, root mean squared prediction error (RMSE), and percentage accurate prediction at hospital admission (ranked by % accurate prediction)

REE predictive equation	REE[1]	SD	Accurate prediction[2]	Under prediction[3]	Over prediction[4]	Bias[5]	Maximum negative error[6]	Maximum positive error[7]	RMSE
	kcal/d		*%*	*%*	*%*	*%*	*%*	*%*	*kcal/d*
REE measured	**1473**	**311**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Lazzer(37)	1421	180	40	35	25	-0.6	-34	104	260
FAOWHO-wh(38)	1372	175	40	42	18	-4.3	-36	91	266
Owen(39;40)	1364	211	40	44	16	-5.1	-36	82	275
Schofield-wh(41)	1337	180	39	48	13	-6.7	-37	85	277
Luhrmann-a(22)	1314	212	38	50	12	-8.6	-39	76	298
Korth(42)	1399	278	37	43	20	-3.4	-43	83	264
Fredrix(21)	1309	232	37	52	11	-9.3	-43	61	297
Muller(43)	1302	234	37	53	10	-9.8	-42	62	303
Luhrmann-b(22)	1291	217	36	55	9	-10.4	-42	64	307
Delorenzo(44)	1284	209	35	58	7	-10.8	-42	66	309
Cole(45)	1286	191	34	58	8	-10.5	-40	70	308
HB1984(46)	1283	195	33	59	8	-10.7	-42	68	310
FAO/WHO-w(47)	1276	179	33	59	8	-10.9	-41	78	324
Henry-wh(45)	1309	189	33	56	11	-12.2	-41	71	331
Muller-bmi(48)	1205	391	33	56	11	-17.4	-73	79	445
Henry-w(49)	1266	199	31	63	6	-12.2	-41	71	329
Schofield-w(41)	1259	164	30	62	8	-12.0	-41	76	336
UK1991(50)	1268	224	30	62	8	-12.1	-45	58	319
Siervo(51)	1235	147	30	63	7	-13.5	-44	78	355
HB1919(52)	1244	200	29	64	7	-13.5	-44	62	339
Mifflin(53)	1221	227	25	70	5	-15.5	-49	57	350
Livingston(54)	1188	220	23	73	4	-17.7	-48	46	378
Bernstein(55)	1013	153	5	93	2	-29.4	-55	39	531

w; including weight in equation
wh; including weight and height in equation
a; including weight and sex in equation
b; including weight, age and sex in equation
[1] As measured
[2] The percentage of subjects predicted by this predictive equation ± 10% of the measured value
[3] The percentage of subjects predicted by this predictive equation > 10% below the measured value
[4] The percentage of subjects predicted by this predictive equation > 10% above of the measured value
[5] Mean percentage error between predictive equation and measured value
[6] The largest under prediction that was found with this predictive equation as a percentage of the measured value
[7] The largest over prediction that was found with this predictive equation as a percentage of the measured value

Table 3: Evaluation of resting energy expenditure (REE) predictive equations in 107 malnourished elderly patients based on bias, root mean squared prediction error (RMSE), and percentage accurate prediction three months following hospital discharge (ranked by % accurate prediction)

REE predictive equation	**REE[1]**	**SD**	**Accurate prediction[2]**	**Under prediction[3]**	**Over prediction[4]**	**Bias[5]**	**Maximum negative error[6]**	**Maximum positive error[7]**	**RMSE**
	kcal/d		*%*	*%*	*%*	*%*	*%*	*%*	*kcal/d*
REE measured	**1448**	**289**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
FAOWHO-wh(38)	1427	172	63	17	20	1.2	-24	51	183
Owen(39;40)	1420	214	60	23	17	0.4	-23	53	189
Schofield-wh(41)	1393	181	57	27	16	-1.3	-25	46	186
Henry-wh(45)	1365	193	57	32	11	-3.4	-26	41	194
Korth(42)	1481	275	57	15	28	4.2	-25	53	205
Luhrmann-a(22)	1377	209	56	31	13	-2.7	-25	47	195
Delorenzo(44)	1352	217	53	36	11	-4.5	-26	43	199
Lazzer(37)	1480	185	53	16	31	5.1	-22	61	194
Fredrix(21)	1380	238	54	33	13	-2.7	-27	51	198
Muller(43)	1371	234	51	37	12	-2.9	-27	50	199
Luhrmann-b(22)	1358	219	51	38	11	-4.1	-26	47	200
Cole(45)	1346	190	51	38	11	-4.8	-26	41	199
HB1984(46)	1345	210	49	40	11	-4.9	-27	46	201
Schofield-w(41)	1307	170	46	44	10	-7.3	-31	39	186
UK1991(50)	1336	230	45	43	12	-5.3	-31	48	218
FAO/WHO-w(47)	1328	187	45	43	12	-5.9	-30	40	223
Muller-bmi(48)	1284	366	44	42	14	-10.3	-59	49	330
Henry-w(49)	1315	207	43	46	11	-5.7	-31	48	221
Siervo(51)	1280	150	42	51	7	-9.0	-34	40	254
HB1919(52)	1307	217	41	50	9	-7.7	-29	42	225
Mifflin(53)	1292	226	38	54	8	-9.0	-32	33	229
Livingston(54)	1256	220	31	62	7	-11.4	-34	39	256
Bernstein(55)	1059	169	8	91	1	-25.0	-44	19	422

w; including weight in equation
wh; including weight and height in equation
a; including weight and sex in equation
b; including weight, age and sex in equation
[1] As measured
[2] The percentage of subjects predicted by this predictive equation ± 10% of the measured value
[3] The percentage of subjects predicted by this predictive equation > 10% below the measured value
[4] The percentage of subjects predicted by this predictive equation > 10% above of the measured value
[5] Mean percentage error between predictive equation and measured value
[6] The largest under prediction that was found with this predictive equation as a percentage of the measured value
[7] The largest over prediction that was found with this predictive equation as a percentage of the measured value

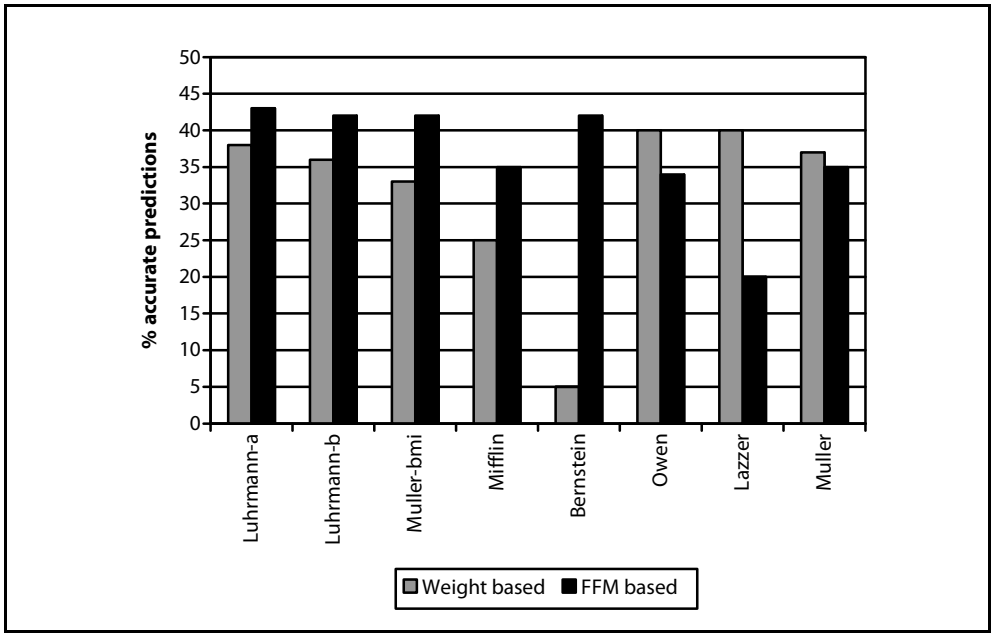

Figure 1a: Comparison of percentage accurate predictions for weight-based compared with fat free mass (FFM)-based resting energy expenditure predictive equations at hospital admission

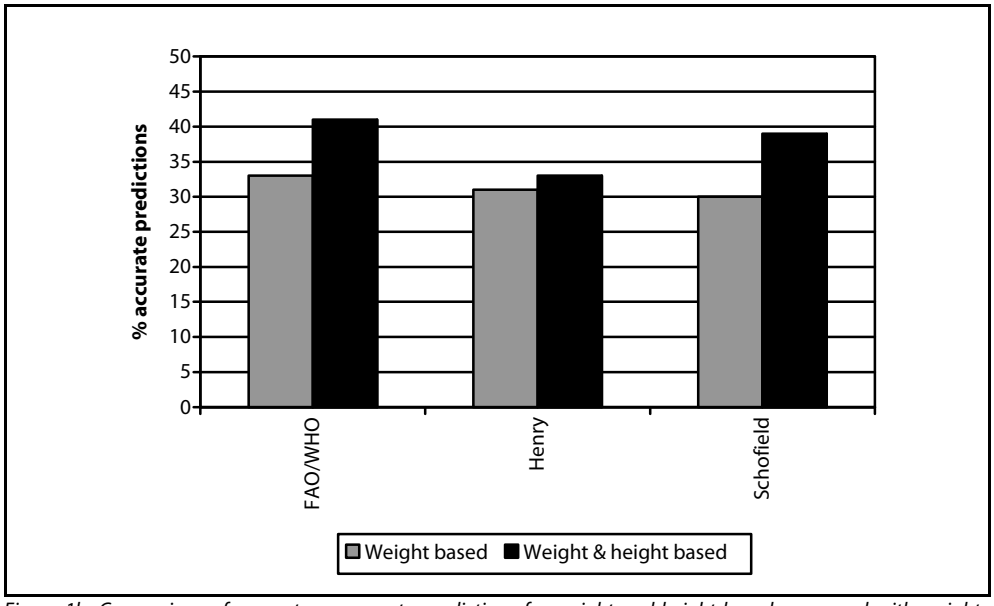

Figure 1b: Comparison of percentage accurate predictions for weight-and-height-based compared with weight-only-based predictive equations at hospital admission

The percentage accurate predictions when corrected with a range of illness factors for measurements at hospital admission for the three best predicting equations is presented in Figure 2. Adding an illness factor of 5% appeared to be sufficient to optimize the percentage accurate prediction. After correction, the accuracy of the best predicting equation (FAO/WHO incl. weight and height) increased from 40% to 47%. Adding an illness factor at three months following discharge did not improve the percentage accurate predictions.

The percentage accurate predictions for a broad range of fixed factors of kcal per kg body weight at hospital admission and three months following discharge is presented in Figure 3.
For the equations the prediction error ranged from 260 to 531 kcal at hospital admission and from 183 to 422 kcal three months following discharge. For fixed factors the prediction error ranged from 305 to 824 kcal at hospital admission and from 243 to 713 kcal three months following discharge.
All equations showed a negative percentage of bias at hospital admission as well as at three months following hospital discharge, which means that all equation under predicted the measured REE.

Bland-Altman plots for the three best prediction equations for REE (Lazzer, FAO/WHO incl. weight and height, Owen) at hospital admission and three months following hospital discharge are expressed in Figure 4. One patient was excluded from the figure because of an outlying measured REE of 2774 kcal at the final measurement. The Bland-Altman plot for FAO and all other predictive equations showed a proportional bias, with overestimation of low REE values and underestimation of high REE values. Retrospectively, this proportional bias was corrected, using regression analysis, which resulted in the expected zero bias (Figure 5). However, no improvement of percentage accurate predictions was obtained by this correction for all equations.

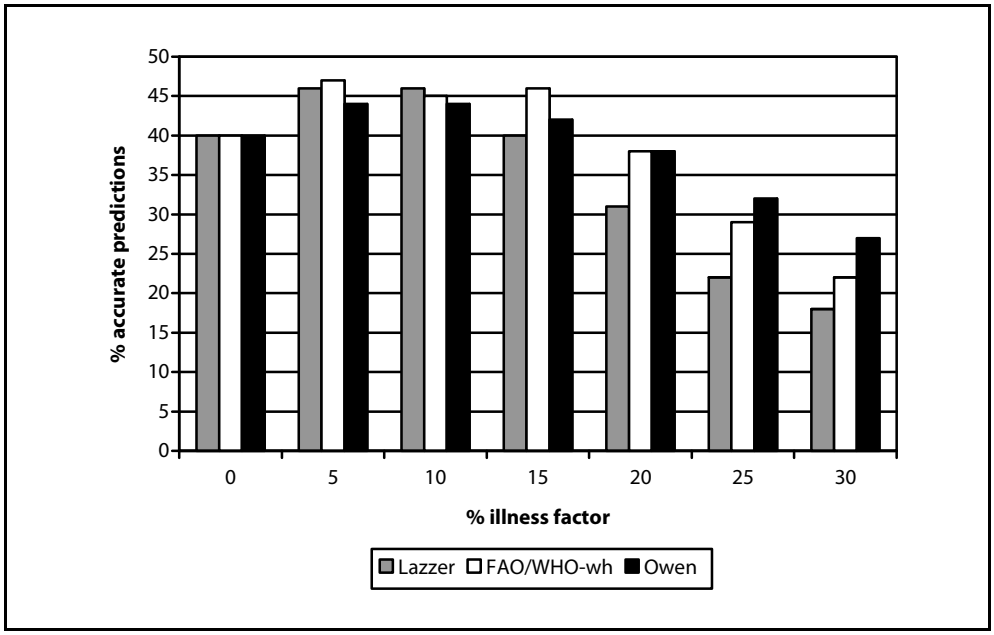

Figure 2: Percentage accurate predictions of a range of illness factors for the three best predicting equations at hospital admission

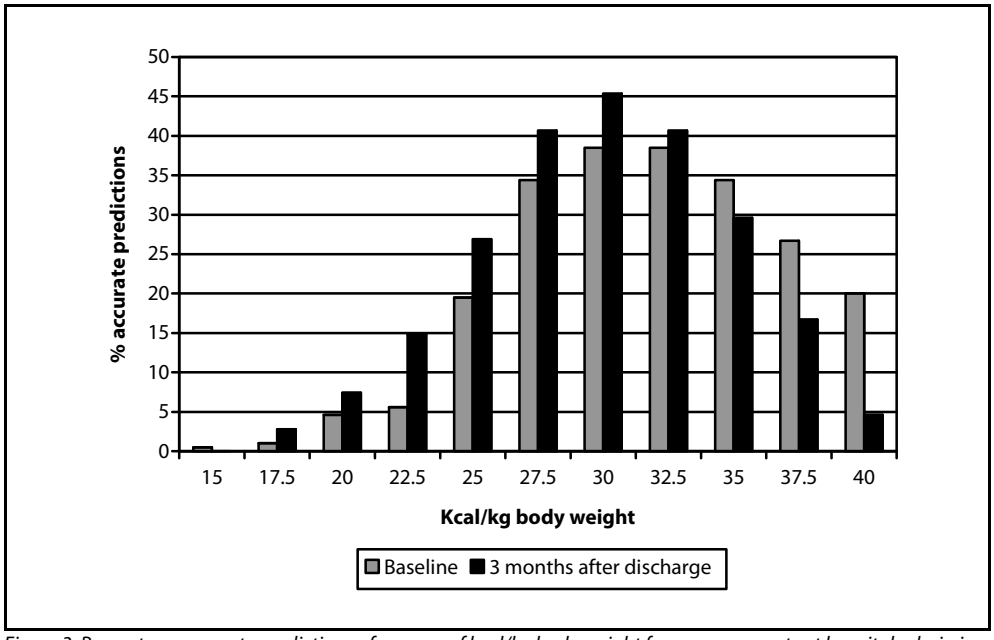

Figure 3: Percentage accurate predictions of a range of kcal/kg body weight for measurements at hospital admission (baseline) and three months following hospital discharge

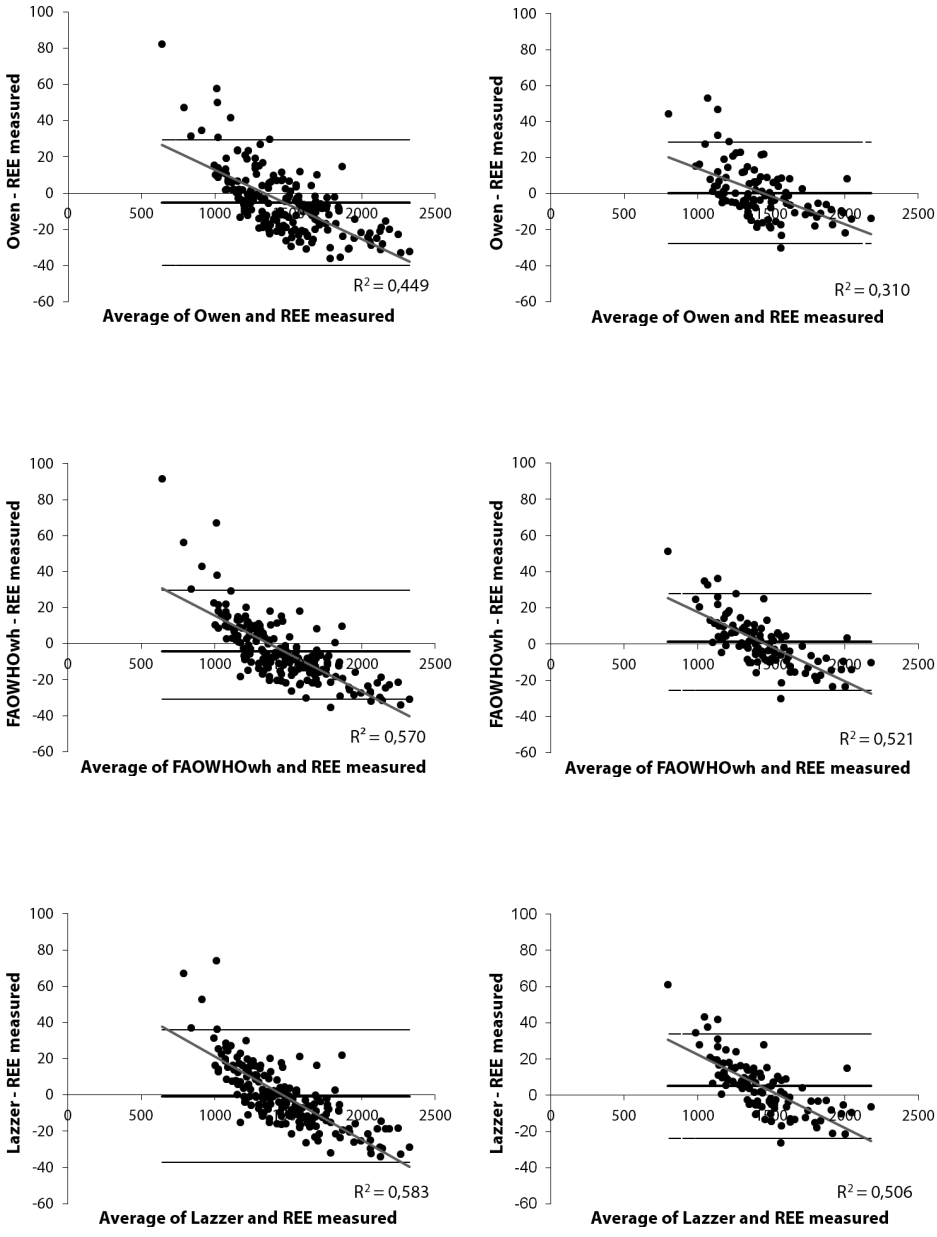

Figure 4: Bland-Altman plots for 3 selected resting energy expenditure (REE) prediction equations (Owen, FAO/WHO-weight and height, Lazzer) at hospital admission (left) and three months following hospital discharge (right)

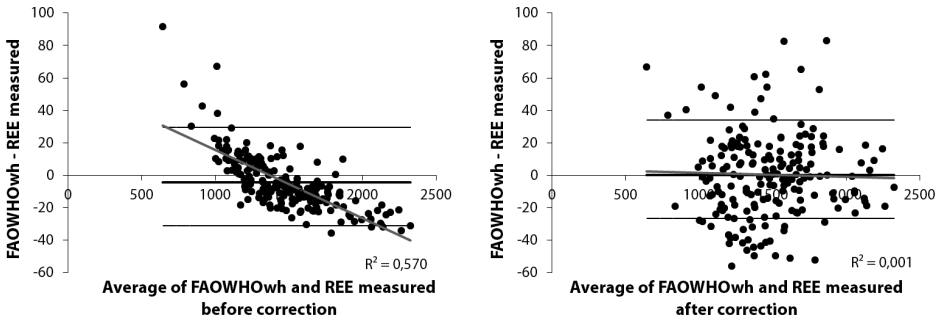

Figure 5: Bland-Altman plots for resting energy expenditure (REE) prediction equation FAO/WHO-weight and height prior to (left) and after (right) correction for the proportional bias by regression analysis

Discussion

Predictions of resting energy expenditure for malnourished hospitalized elderly patients during admission to hospital appear to be subject to large errors, with the best thus far developed prediction equations predicting only 40% of patients accurately. When patients are reassessed three months following discharge, their body weight and health status improved, the best equations predicted 66% of patients accurately. Our data suggest that prediction accuracy is inversely related to poor nutritional status and disease. However, even after (partial) recovery the prediction accuracy remains marginal. Fixed factors (kcal/kg) or the use of fat free mass assessment do not improve the results.

Predictive equations have generally been developed in healthy populations or in critically ill patients, on the basis of regression analysis of body weight, height, sex, and age as independent variables and measured REE by indirect calorimetry as a dependent variable. In healthy overweight and obese adults the best prediction equation showed 79% accuracy (26), and in an even more varied weight group from normal weight to extreme obesity in women 71% accuracy could be reached(29).
In hospitalized underweight critically ill patients 42% accuracy could be reached(30). However, severely underweight patients with body weight below 50 kg were very difficult to predict accurately(31). Earlier we showed similar poor results for inpatients, but not primarily due to underweight patients(14). Equations based on elderly are rather scarce(21;22). In a review, specifically focussing on elderly, Gaillard et al.(24) concluded that the Harris-Benedict and FAO/WHO predictive equations were the most accurate. However, this conclusion was drawn based on the results of bias only, which is an incomplete method of evaluating adequate predictions. Boullata et al.(32) evaluated hospitalized adult patients (18-92 y), but included 36% ventilated intensive care patients

(61% accurate prediction). Compher et al.(33) evaluated hospitalized elderly African Americans, but this population is not comparable to ours (26% accurate predictions). Melzer et al.(15) showed that healthy elderly (≥ 70 years) had 72% accurate predictions, suggesting that being old per se is not the main cause of the poor accuracy.
For elderly Bosy-Westphal et al. (34) described that there was a proportionate decrease in FFM, with no specific adaptations in organ mass energy expenditure. However, for more acute weight loss, they describe variable loss of organ mass and an accompanying broader range in energy expenditure. This might explain in part the very large range in REE (641- 2325 kcal/24h) in the present study.

Our study demonstrated that a fixed factor (kcal/kg) was not better than other equations. Within the range of fixed factors, 30 kcal/kg performed best. This is slightly higher than the 27.5 kcal/kg (≈ 21-22 kcal for REE + 30% stress/illness/activity factor) suggested by Gailliard et al. and Alix et al.(23;24). The difference can possibly be explained by the poorer health status and the poorer nutritional status of our patients.

Our population is heterogeneous and differed in nutritional status, age, medical diagnosis, and health status. Prediction equations do not adjust for these differences. Some examples: all patients were malnourished at time of the measurement of REE at admission to the hospital. However, there was a wide variation in degree of malnutrition as shown in the results. Some patients presented with chronic weight loss, while others had acute weight loss. Overall this is a very representative group of patients the REE predictive equations is needed for.
Another explanation in the broad range of REE could be found in the medical diagnoses. Although most patients were admitted to the department of internal medicine, they suffered from a wide range of medical diagnoses. Adding an illness factor of 5% only slightly optimized the percentage accurate predictions. Inflammation was expected to explain part of this illness factor. However, in post-hoc analyses REE's in patients with elevated CRP levels were not higher than REE's in patients with normal levels (data not shown). The illness factor can probably better be regarded as a correction factor for, for instance, malnutrition.
The difference in accuracy of REE between three months following discharge compared to hospitalisation is hypothesized to be due to an improved health state of our patients. In an earlier study it was demonstrated that patients receiving a three months nutritional intervention (containing extra energy, protein and vitamin D, supported by dietetic counselling) significantly improved their body weight and significantly decreased their functional limitations in the three months following discharge(35). Recovery of body weight might have increased REE and recovery from illness might have

decreased REE at the same time, thus explaining why we did not observe a difference in REE between admission and three months following discharge(36). Adding an illness factor to the prediction equations at three months did no longer improve the percentage accurate predictions. At three months following discharge prediction equations showed only a moderate accuracy of 63%. The majority of patients were still in a suboptimal health, which may possibly explain the poor predictions.
Equations including data on fat free mass or height did not always improve the results. Both measuring fat free mass and measuring height are unpractical and time consuming measurements in this patient group; FFM because of the need of extra equipment and height because of the ill, old, frail and frequently bed rested population. Although the measurement of body composition can be valuable, it does not appear to be necessary to improve REE predictions.

From literature it can be concluded that REE was measured after an overnight fast (Alix et al.(23), Melzer et al.(15)), four-hour fast (Compher et al.(33)) or two-hour fast (Boullata et al.(32)). In the present study patients were not fully post-absorptive prior to measuring resting energy expenditure by indirect calorimetry. This could have increased the resting energy expenditure compared to studies with measurements after overnight fasting. On the other hand, this is daily practice. With only a few exceptions (16/196 baseline measurements) REE was measured more than 2 hours following oral dietary intake.
Mean REE measurement of 1473 kcal/d (men: 1636 kcal/d, women: 1331 kcal/d) for malnourished ill elderly patients in our study is quite similar to results by Alix et al. (total group: 1560 kcal/d, men: 1748 kcal/d, women: 1430 kcal/d)(23), Compher et al. (total group: 1391 kcal/d)(33), Melzer et al. (total group: 1370 kcal/d, men: 1462 kcal/d, women: 1262 kcal/d)(15) and Boullata et al. (total group: 1617 kcal/d)(32).

Most equations seemed to under predict REE. In malnourished patients this is undesirable and hindering adequate recovery. Therefore, measuring body weight to monitor adequacy of nutritional support is of major concern in these patients.

Conclusion

From these results it can be concluded that REE prediction equations and fixed factor of kcal/kg/d are not adequate for hospitalized malnourished elderly patients. Therefore, the suggesting is made to always measure energy expenditure in this group of patients. However, measuring resting energy expenditure by indirect calorimetry is hardly feasible in most clinical settings, due to time consuming measurements, lack of trained personnel, and expensive equipment. More effective and accurate, bedside equipment to measure REE would therefore be welcome, but is not yet available. Meanwhile, a new REE prediction equation for malnourished elderly patients could be developed.

For daily practice, it is strongly advised to monitor body weight after the start of nutritional intervention, because this study demonstrates that prediction equations or fixed factors of kcal/kg, are too small a basis for establishing reachable dietary goals.

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CHAPTER 8

Should we feed malnourished cognitively impaired hospitalized elderly patients?

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Should we feed malnourished cognitively impaired hospitalized elderly patients?
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Abstract

Background

In our society offering extra nutritional support is a standard for malnourished patients at admission to hospital. Whether malnourished, cognitively impaired, hospitalized, elderly patients would also benefit from this regimen is unknown. This study assesses their three- months and one-year survival. Prognostic characteristics predicting life-expectancy are also studied.

Methods

This prospective cohort included malnourished, cognitively impaired, hospitalized, elderly patients (group 1: dementia, 2: delirium and 3: combination dementia/delirium) newly admitted to an acute hospital and receiving usual nutritional care. Data on survival was completed until one year following patients' admission to the hospital. Possible prognostic characteristics predicting life-expectancy data were collected.

Results

A cohort of 116 malnourished, cognitively impaired, hospitalized, elderly patients is described. Forty-nine patients were described to have dementia, 48 delirium and 19 a combination of dementia and delirium. Mean age was 81.6 years (SD 8.3, range 60-99 years). Fifty-five patients (47.4%) died within one year following hospital admission, 36 of them (31%) died within three months following hospital admission. There were no significant differences in survival between the three groups (p=0.672)

Patients with a malignancy or vascular disease were more likely to die within three months following discharge.

Conclusion

Almost half of a cohort of malnourished, cognitive impaired, hospitalized, elderly patients died within one year following hospital admission. Patients with a malignancy or vascular disease were more likely to die early following discharge. It could be defended that in these patients, extra nutritional support should no longer be offered as a standard.

Background

The incidence of people with dementia increases as the demographic profile of the population shifts towards older people(1). In the western world, more than 5% of the people over 60 years of age have some form of dementia(2-5).

Dementia is a disorder that is characterized by impairment of memory and at least one other cognitive domain (aphasia, apraxia, agnosia and /or executive function). These must represent a decline from previous level of function and be severe enough to interfere with daily function and independence. Malnutrition is associated with dementia and often even preceding dementia(6-8). Oral nutritional intake is often inadequate due to impaired ability to complete motor and perceptual tasks required for eating and often prevent the older adult from accepting help with feeding from caregivers(9;10).

Mortality rates in patients with dementia (≥ 60 years of age) are more than three times higher in the first year following diagnosis than in those without dementia(10;11).

In direct contrast to dementia, which is a chronic confusional state, delirium is an acute confusional state and typically its duration is short. Delirium is characterized by four key features: 1) disturbance of consciousness with reduced ability to focus, sustain, or shift attention 2) a change in cognition or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established, or evolving dementia 3) the disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day and 4) there is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by a medical condition, substance intoxication, or medication side effect(12).

Acutely hospitalized, elderly patients depict the highest delirium incidence and the lowest delirium detection rate. Delirium is especially under-diagnosed in demented patients, while dementia is the strongest risk factor for delirium(13;14).

In well-conscious, malnourished elderly patients, not terminally ill, standard nutritional therapy would be considered if life expectancy would exceed three months(15;16). Keeping in mind the increased mortality rates of cognitively impaired patients, the question whether or not to start intensive nutritional therapy, e.g. oral nutritional supplements or enteral tube feeding, for a longer period of time in these patients remains yet to be answered. Research addressing this difficult issue is lacking. Therefore, the aim of this study is to describe three-months and one-year survival in malnourished, cognitively impaired (dementia, delirium or a combination of both), hospitalized, elderly patients. In addition, possible prognostic characteristics predicting life-expectancy will be studied. Most ideally, this would identify those who live longer or may have other benefits (function, quality of life) if nutritional intervention is started.

Methods

The present study was designed as a secondary analysis of a previously conducted study which has been reported elsewhere(17). The present study describes the nutritional and clinical status and the three-months and one-year survival of malnourished, cognitively impaired, elderly patients acutely admitted to a hospital. In the parent study, a randomized controlled trial, 575 elderly patients were identified as malnourished(17) and eligible to be randomized to receive extra individualized nutritional support or usual care(18). Hundred and sixteen (20%) of them were cognitively impaired (suffering from dementia and/or delirium) and for that reason excluded from the parent trial, being unable to answer the questions and to follow measurement assignments. They were treated for their underlying medical diagnosis and offered standard nutritional care according to best practices.

This secondary study focuses on these cognitively impaired patients. The study was approved by the Medical Ethics Committee of the VU University Medical Center Amsterdam.

Population

Men and women aged 60 and older and admitted to the VU University Medical Center for at least two days at the specialties general internal medicine, gastroenterology, nephrology, orthopaedics, traumatology and vascular surgery were eligible to participate.

In this secondary study the prognosis of patients with a combination of 1) malnutrition and 2) cognitive impairment is described.

Malnutrition

For the initial parent study, we screened 3291 patients for the presence of malnutrition. Given the large number of patients to be screened, we chose a quick reference standard for the definition of malnutrition: 1) Body Mass Index (BMI in kg/m^2) < 20 and/or 2) ≥ 5% unintentional weight loss in the previous month and/or 3) ≥ 10% unintentional weight loss in the previous six months. Body weight was measured, with patients wearing light indoor clothes and no shoes, on a calibrated electronic scale (Prior MD-1512, Seca, Hamburg, Germany), with an accuracy of 0.1 kilogram. A correction factor for clothes was made by deducting weight with 2.0 kilograms for men and 1.3 kilograms for women(19). As measurement of height is often not feasible in this hospitalized, frail, elderly population, data on height was derived from medical records or by proxy. BMI was calculated as actual weight in kilograms divided by the square of height in meters.

As described, patients in this secondary study were excluded from the parent study due to cognitive impairment. They received usual nutritional therapy during admission and

post-discharge. Although some of the patients probably received additional nutritional therapy, this was not provided systematically, not continued following discharge from the hospital and not documented.

Cognitive impairment
Patients were clarified cognitively impaired if either dementia or delirium or a combination of dementia and delirium was diagnosed by the treating physician or in a referral letter from patient's general practitioner or nursing home physician. As this study was designed as a secondary analysis of a parent study, it was not possible to prospectively collect data on neither the stage nor the type of dementia. Routinely used screening, assessment and diagnostic tools, like MMSE or CAM were therefore not available for the patients described in this study.

Survival
Post-discharge data on survival was completed until one year following patients' admission to the hospital. The patient information system of the VU University Medical Center was used and general practitioners were contacted for mortality dates.

Predictors of survival
To study possible prognostic characteristics predicting life-expectancy prospective data were collected from the patients, their medical records and/or the department for finance, health information management and health administration of the VU University Medical Center.
Data on:

- general patient characteristics (gender and age),
- anthropometric measurements (body weight, height, BMI, weight change in the last month and last six months),
- home situation (i.e. living independently or nursed),
- given child birth,
- residence prior to admission and following discharge (living at home without additional care, or nursed, living at nursing homes, homes for the elderly, rehabilitation clinics or psychiatric hospitals),
- primary diagnosis at hospital admission,
- nature of cognitive impairment (dementia, delirium or a combination of dementia and delirium),
- biochemical parameters at admission (albumin (g/L), CRP (mg/L), leukocyte (*10^9/L), haemoglobin (mmol/L), calcium (mmol/L), kreatinin (µmol/L)), systolic-

and diastolic blood pressure (mmHg) at admission, body temperature (Celsius) at admission and pulse rate (min) were collected at admission.

The 116 included patients were admitted to the hospital with 73 different medical diagnoses. Based on medical expert's opinion we categorized the medical diagnosis into 11 main categories (Table 1).

Table 1: Baseline and clinical characteristics

Characteristics	**Total (n=116)**	**Dementia (n=49)**	**Delirium (n=48)**	**Dementia and delirium (n=19)**	***p*-value between three groups**
Sex, no. females (%)	77 (66.4)	30 (61.2)	37 (77.1)	10 (52.6)	0.097
Age in y, mean (± SD)	81.2 (8.3)	79.8 (7.3)	81.5 (10.1)	83.7 (4.9)	0.095
Home situation, no. (%)					0.202
Living alone	77 (67.5)	36 (75.0)	31 (66.0)	10 (52.6)	
Living with partner/family	37 (32.5)	12 (25.0)	16 (34.0)	9 (47.4)	
Giving child birth, no. ≥ 1 child (%)	86 (74.1)	35 (71.4)	36 (75.0)	15 (78.9)	0.636
Residence preadmission, no. (%)					0.953
Independently	89 (76.7)	37 (75.5)	37 (77.1)	15 (78.9)	
Nursed	27 (23.3)	12 (24.5)	11 (22.9)	4 (21.1)	
Residence following discharge, no. (%)					0.637
Living independently	43 (44.8)	21 (50.0)	15 (39.5)	7 (43.8)	
Nursed	53 (55.2)	21 (50.0)	23 (60.5)	9 (56.3)	
Duration of admission in days (± SD)	16.16 (17.2)	14.4 (13.1)	14.3 (10.0)	25.5 (32.6)	0.214
Body Mass Index in categories, no. (%)					0.671
BMI ≤ 20	81 (69.8)	34 (69.4)	35 (72.9)	12 (63.1)	
BMI 20-25	27 (23.3)	11 (22.4)	10 (20.8)	6 (31.6)	
BMI ≥ 25	8 (6.9)	4 (8.2)	3 (6.3)	1 (5.3)	
Weight change last month, % (± SD)	-5.3 (6.5)	-5.9 (7.1)	-4.4 (6.3)	-6.2 (5.6)	0.271
Weight change past 6 months, % (± SD)	-10.3 (8.3)	-10.9 (6.6)	-9.7 (9.2)	-10.4 (9.4)	0.717
Medical specialty, no. (%)					0.074
Surgical	21 (18.1)	7 (14.3)	13 (27.1)	1 (5.3)	
Nonsurgical	95 (81.9)	42 (85.7)	35 (72.9)	18 (94.7)	
Admission condition, no. (%)					0.706
Acute	83 (71.6)	35 (71.4)	33 (68.8)	15 (78.9)	
Chronic	33 (28.4)	14 (28.6)	15 (31.2)	4 (21.1)	

Table 1: (continued)

Characteristics	Total (n=116)	Dementia (n=49)	Delirium (n=48)	Dementia and delirium (n=19)	*p*-value between three groups
Primary diagnosis in categories, no. (%)					0.665
Infection	39 (33.5)	16 (32.7)	14 (29.1)	9 (47.3)	
Heart failure	3 (2.6)	3 (6.1)	-	-	
Vascular disease	6 (5.2)	4 (8.2)	1 (2.1)	1 (5.3)	
Kidney insufficiency	5 (4.3)	2 (4.1)	2 (4.2)	1 (5.3)	
Fractures, orthopaedic disorders	17 (14.7)	5 (10.2)	12 (25.0)	-	
Malignant neoplasm	8 (6.9)	4 (8.2)	4 (8.3)	-	
Chronic bowel disease	3 (2.6)	1 (2.0)	1 (2.1)	1 (5.3)	
Diabetes mellitus	5 (4.3)	1 (2.0)	1 (2.1)	3 (15.8)	
Bleeding in gastrointestinal tract	9 (7.8)	6 (12.2)	2 (4.2)	1 (5.3)	
Liver, gall, and pancreas insufficiency	2 (1.7)	-	2 (4.2)	-	
Other	19 (16.4)	7 (14.3)	9 (18.7)	3 (15.7)	
Albumin (g/L)	31 (5.2)	31 (5.1)	29 (5.2)	33 (4.3)	**0.025**
Leukocytes (x10^9/L)	13.2 (11.3)	12.1 (7.1)	12.5 (6.3)	17.6 (23.6)	0.776
CRP (mg/L)	82 (97.2)	72 (80.2)	88 (99.9)	93 (127.3)	0.814
Haemoglobin (mmol/L)	7.2 (1.3)	7.1 (1.4)	7.1 (1.3)	7.9 (0.9)	**0.039**
Calcium (mmol/L)	2.26 (0.2)	2.23 (0.2)	2.22 (0.3)	2.41 (0.2)	**0.002**
Corrected calcium (mmol/L)*	2.43 (0.2)	2.40 (0.2)	2.41 (0.3)	2.53 (0.2)	**0.030**
Kreatinin (µmol/L)	149.0 (127.9)	146.0 (130.7)	162.4 (142.9)	119.8 (46.5)	0.744
Systolic BP (mmHg)	136 (27.2)	129.6 (27.2)	138 (28.6)	148 (18.2)	0.072
Diastolic BP (mmHg)	76 (20.5)	76 (27.2)	76 (16.1)	74 (7.6)	0.613
Pulse rate (min)	91 (23.2)	96 (26.3)	86 (22.8)	89 (11.3)	0.426
Temperature (º Celsius)	37.1 (1.1)	37.3 (1.1)	37.0 (1.1)	37.0 (1.1)	0.402

** Corrected calcium = measured calcium + 0.020 (40 - measured albumin)*

Statistical analyses

Standard descriptive statistical methods were used to express means, standard deviations, percentages, frequencies, changes in variables and minimum and maximum values. Differences in patient characteristics between the three groups with dichotomous variables, categorical variables and continues variables were analyzed by chi-square tests, ANOVA tests and Kruskal-Wallis tests, respectively. Statistical significance was defined at $p < 0.05$**.**

Kaplan-Meier curves were used to estimate the three-months survival and one-year survival function for demented patients, patients with delirium and patients with a

combination of dementia and delirium. Log rank tests were used to compare survival curves for groups of patients with different patient characteristics.
For identifying the best combination of variables predicting survival, cox proportional hazards analysis was conducted, with three months survival and one-year survival as time variable, and three months and one year deceased as status variable and the potential predictors as covariates. Statistical significance was defined at $p < 0.1$.
Statistical analyses were performed using the SPSS-system for Windows, version 17.0 (SPSS, Chicago, IL, USA).

Results

In total 116 malnourished cognitively impaired hospitalized elderly patients were included in this study. Forty-nine patients were described to suffer from dementia, 48 from delirium and 19 from a combination of dementia and delirium. Mean age was 81.6 years (SD 8.3, range 60-99 years) and 66.4% of patients were female.
Baseline and clinical characteristics are presented in Table 1. *P*-values demonstrate the differences between the three groups (dementia, delirium and the combination of dementia and delirium). At baseline, no statistically significant differences in characteristics between groups could be demonstrated, except for albumin (p=0.025), haemoglobin (p=0.039), calcium (p=0.002) and corrected calcium (p=0.030). The most common admitting diagnosis was infection (67%).

Survival

Thirty-six patients (31%) died within three months following hospital admission and 55 patients (47.4%) died within one year following hospital admission. Classifying for dementia, delirium and the combination of dementia and delirium resulted in three-month death rates of 12 patients (25%), 19 patients (40%) and 5 patients (26%), respectively (NS, p=0.234). One year death rates were 21 patients (43%), 27 patients (56%) and 7 patients (37%), respectively (NS, p=0.223). The accompanying Kaplan-Meier curve to express one-year survival is presented in Figure 1.

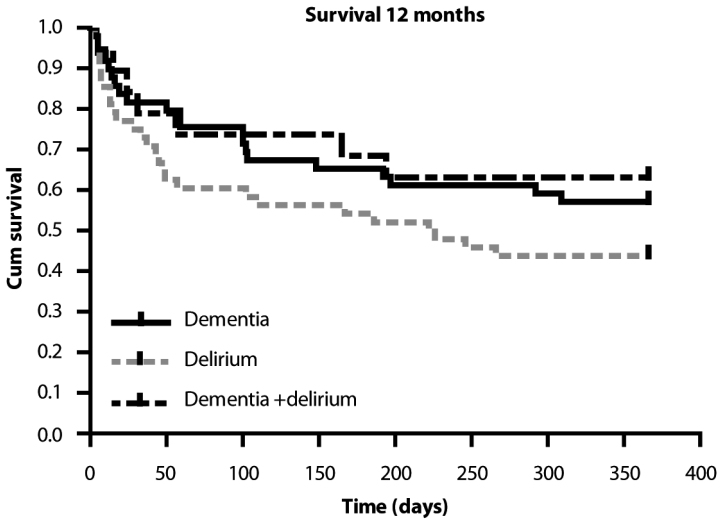

Figure 1: Kaplan-Meier curve expressing one-year survival in malnourished elderly patients with dementia, delirium and a combination of dementia and delirium (p=0.223)

Predictors of death

The univariate associations between potential predictors of death at three months and one year are shown in Table 2.

The multivariate Cox proportional hazard model including the identified potential predictors of deceases 'exploded'. This was caused by the high mortality rates of patients with malignant disease (7/8 within three months and 8/8 within one year) and vascular disease (4/6 within three months and 5/6 within one year).

Decision was therefore made to repeat the complete statistical analyses without the primary medical diagnosis of the patient. Log rank test then revealed albumin (p=0.04), age (p=0.085), BMI (BMI ≤ 20 p=0.66; BMI 20-25 p=0.85 ; BMI ≥ 25 p=0.46) and given child birth (p=0.133) to be possible predictors of death after one year. In the multivariate Cox proportional hazards only albumin remained significant.

Table 2: Univariate association between potential predictors and death following three months and one year

Characteristics	3 months, *p*-value	One year, *p*-value
Malignant neoplasm	0.003	0.002
Vascular disease	0.018	0.049
Fractures	0.022	0.003
Being a widow	0.030	0.043
Albumin	0.045	0.003
Living alone	0.056	†
Systolic blood pressure	0.059	†
Heart failure	0.061	†
Age	0.082	0.042
Given child birth	†	0.074
BMI ≤ 20	†	0.088
BMI 20-25		0.064
BMI ≥ 25		0.100

† *No potential predictor of death following three months or one year survival*

Discussion

In this study, patients with a multi-morbidity consisting of malnutrition, cognitive impairment, old age and an illness requiring hospitalisation were shown to have a high mortality rate within three months and one year following admission to the hospital.

The clinical relevance of the decision whether or not to offer extra intensive nutritional therapy to this specific group of patients is high since this applies to approximately twenty percent of the malnourished hospital admitted elderly patient population(17;20). In our society, offering extra nutritional therapy is a standard for all patients identified malnourished at admission to hospital. This has even been defined a quality indicator by the Dutch ministry of Health, Welfare and Sport. Earlier studies demonstrated that it takes at least three months for nutritional therapy to be effective, probably even longer(15). This was confirmed by our parent study including malnourished, hospitalized, elderly patients without cognitive impairment(17). A significant decrease in functional limitations, though not in other functional outcomes, was demonstrated following three months of nutritional intervention, suggesting that the intervention had probably not lasted long enough.

Good et al., in their Cochrane review on medical nutrition in palliative care(16), suggest that patients with a good performance status and medium to long-term prognosis (months to years) might possibly benefit from extra nutritional intervention. However, the evidence to support this suggestion is weak. For our specific study population with

multi-morbidity and a relatively short life-expectancy, it could perhaps be defended that extra, individualized nutritional therapy, in addition to usual nutritional care, should no longer be offered as standard care(10).

This study shows that subgroups of patients with multi-morbidity were likely to die early following discharge when receiving usual nutritional care. It is unsure whether optimal nutritional therapy in this specific group of patients would have influenced other endpoints, such as quality of life. Measuring quality of life in this group carries its limitations because of the cognitive impairment. We doubt whether nutrition intervention studies aiming at these endpoints will be designed in the near future. If we would make the decision that optimal nutritional care is required for these specific patient groups, tube feeding could be a solution to rely on. We would than have to face the ethical question whether or not to give this type of nutritional support. Therefore, according to the current scientific state, our suggestion would be to carefully re-consider our standard regimen to offer intensive nutritional therapy, e.g. oral nutritional supplements or tube feeding, to these patients.
Data are lacking to explain the early deaths in patients with a diagnosis of vascular disease and malignancy. It could be hypothesized that these patients have a more extensive medical history with several co-morbidities than others and that this decreased survival in these patients.

This study had certain limitations. First of all, malnutrition was identified by a reference standard of a reduced BMI and/or unintentional weight loss. Although the increased mortality risk of low BMI values is well established for elderly people, cut-off points for BMI in elderly people are debated. We chose a strict cut-off point of 20, to be sure of a true risk of undernutrition.
In elderly people, malnutrition can be regarded as a geriatric syndrome, consisting of multiple co-morbidities and risk factors on the somatic, mental, functional and social domain. For that reason, one could argue that the MNA(21) would be a more appropriate instrument for the risk screening. However, more than 3000 patients, admitted to different medical wards, were initially screened. Applying the MNA was a too time-consuming task. We chose a, in our opinion, second best alternative, i.e. BMI and unintentional weight loss.
Secondly, dementia and delirium were not diagnosed or standardized by MMSE, CAM or other screening or assessment tools. This study was designed as a secondary research question. We observed a 20% exclusion rate from the parent study, due to cognitive impairment, only after we had finished the initial study. However, neither dementia nor delirium were systematically assessed. Classification based on referral letters is known to

have a low sensitivity. In addition, many patients with either problem were probably not included in the study (22;23) and one can expect those to be the healthiest group with cognitive problems. Therefore, the findings of this study must be interpreted with great caution.
Thirdly, classification of diseases is very difficult(24). The medical diagnosis malignancy was beyond doubt, although it included different tumours and different stages. The diagnosis vascular disease was even more controversial. To be able to study the effect of disease on outcome, we had to categorise medical diagnoses (from 73 into 11 categories), which caused loss of information. On the other hand, differences were found between clustered-diagnose-groups, in which it is harder to demonstrate differences than in large single-diagnose-groups with wide confidence intervals.
Fourthly, we frequently missed data in patients' medical record for specific parameters, e.g. data on blood pressure, pulse and temperature was absent in 44, 47 and 49 patients, respectively. Finally, this study was designed as a secondary study next to a parent study. We described only a relatively small patient cohort. This study does, therefore, not provide a strong level of evidence and conclusions should only be interpreted as recommendations.

Conclusion

Despite these limitations, this study suggest that malnourished, cognitively impaired, and acutely hospitalized elderly patients with a medical diagnosis of malignancy and vascular disease are possibly to die early following hospital discharge. If this is indeed the case, offering intensive nutritional therapy to these patients should perhaps not be given highest priority. In other medical diagnosis nutritional support should be carefully re-considered in the light of perceived benefits and health care costs in individual patient circumstances.
This paper does not have the scientific value to draw sound conclusions, however, it may open a door to discussion and to more research in this area. This would most ideally provide us with tools to identify patients who have a higher probability of living longer or benefiting from nutritional intervention.

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CHAPTER 9

General discussion

Introduction

The aim of this research project was to study the effectiveness and cost-effectiveness of post-discharge nutritional support in malnourished elderly patients, from hospital admission up until three months following discharge.

This chapter summarizes the study results which are presented in this thesis. Furthermore, the results will be discussed more deeply, methodological considerations will be made and future recommendations for both research and clinical practice will be provided.

Firstly, three studies assessed the effect of a post-discharge multi-component nutritional intervention in malnourished ill and elderly patients on functional outcomes, falls and immune function. Secondly, the cost-effectiveness of the nutritional intervention on functional outcomes was studied. Thirdly, another study compared measured values of resting energy expenditure to frequently used predictive equations. Finally, survival of malnourished, cognitively impaired, ill and old patients was studied.

Summary of main findings

Effectiveness

Evidence shows that body weight increased more following a three month post-discharge multi-component nutritional intervention than without; this was significant for patients in the highest body weight category, but not significant in those with lower body weight. Functional limitations decreased more in the intervention group than in the control group. No statistically significant differences could be demonstrated for physical performance, physical activities, fat-free mass, or handgrip strength (Chapter 3).

Patients in the intervention group increased their energy intake, protein intake and serum 25-hydroxy vitamin D compared to patients in the control group. The number of patients who had experienced falls and the mean number of fall incidents showed a decrease in patients in the intervention group, compared to patients in the control group (Chapter 5).

In an exploratory study on a malnourished, ill and elderly patient group, following a three month nutritional intervention, we were unable to demonstrate differences in immune markers, endocrine markers and a selection of micronutrients (Chapter 6).

Cost-effectiveness
Alongside a significant decrease in functional limitations we were able to demonstrate that the given nutritional intervention was cost neutral. There were no differences in health care costs between groups. For functional limitations we found a 0.95 probability that the intervention is cost-effective in comparison with usual care for ceiling ratios > € 6500. Cost-effectiveness could not be demonstrated for quality of life and physical activities (Chapter 4).

Resting energy expenditure; predictive equations versus measurements
Predictions of resting energy expenditure for malnourished ill elderly patients during hospitalization appeared subject to significant errors. The best developed prediction equations, thus far, predicted only 40% of patients accurately. When patients were reassessed three months following discharge, their body weight and health status improved, showing that the best equations predicted 66% of patients accurately (Chapter 7).

Survival in malnourished cognitively impaired patients
From a sub-analysis in malnourished, cognitively impaired, elderly, and acutely hospitalized patients we concluded that patients with a medical diagnosis of malignancy and vascular disease were possibly more likely to die early following hospital discharge than those without these conditions (Chapter 8).

Methodological considerations and recommendations for future research

Patients
Malnutrition is one of the factors that contribute to the progression of functional decline. In later stages of this process towards disability, functional decline may on its turn contribute to the development of poor nutritional status. Consequently, a vicious circle might develop. To study if optimal nutritional care is (cost-)effective, a careful selection of patients is desirable.

We tried to include a study population as homogeneous as possible by including patients from only two wards of the VU University Medical Center in Amsterdam and by excluding patients with malignancies and major bowel surgery, among with accompanying treatments and risk of complications. In spite of that, patients' medical diagnosis, nutritional status, age and health status varied. In future, a trial including a

more homogenous patient group would be preferable, however this would probably need a multicenter approach.

Outcome measures
For this study we collected data from questionnaires, measurements and blood samples. Unfortunately, we encompassed a problem, a lot of data that required a visit to the hospital three months following discharge, i.e. the measurements of body composition, function and blood samples, was missing. Although it was not required to provide a reason for cancellation, most patients indicated that they were too ill or weak to visit the hospital. Future studies could better anticipate on this problem by providing routine visits to patients' home.
We have planned to study differences in survival between the intervention group and control group. Resulting from the above mentioned it will be interesting to study whether patients without follow-up data were indeed the more severely ill patients, and whether they will have higher mortality rates than patients with complete follow-up.

Due to patients' frequently poor health status, it may be considered that the chosen questionnaires were found not to be the most optimal for our study population. The LASA questionnaires on functional limitations, physical activity and the measurements on physical performance were developed in community-dwelling elderly and not in a patient population.
On the one hand, recent literature suggests focussing on gait speed measurements(1;2) as a measure of frailty and as an important prognostic parameter. This literature is convincing, but on the other hand, the measurement has the same limitation in that it will be difficult to perform this test among patients with poor health status.

Measurements on fat free mass sometimes revealed 'errors', resulting in lost data. From a subjective view point we observed that these errors mostly occurred in the most severely malnourished patients. Although no literature is available on these 'errors', more research groups have faced this problem, very often in patients with an extreme body composition, for example the severely malnourished or the well trained athletes with low BMI's, We hypothesize that the modelling software in the equipment deranges when body composition deviates too much from the standard. However, research is necessary to study this hypothesis in more depth.

Malnutrition
In this study, malnourished patients were identified according to the following criteria: a body mass index (BMI) < 20 kg/m^2 and/or ≥ 5% unintentional weight loss in the previous

month and/or ≥ 10% unintentional weight loss in the previous six months(3;4). The cut-off points for malnutrition were derived from the best available literature. After all, nationally and internationally there is no consensus on the definition for malnutrition. For BMI, we have chosen the lowest, most often in literature described cut-off point of 20, ensuring of a true risk of malnutrition(5). For weight loss we relied on studies that revealed associations between percentage involuntary weight loss and poor prognosis(6).

Recently, the Health Council of The Netherlands released a report on malnutrition in the elderly. Factors which play an important role in defining malnutrition, such as BMI and unintentional weight loss were discussed. There should be a causal relationship with a negative prognosis, on for example mortality, to establish these measures as a gold standard for malnutrition. The report also states that, according to the available literature, no clear cut-off value for BMI to define malnutrition in elderly can yet be determined. Other outcome parameters, such as functional outcomes, could be relevant, but unfortunately, there is a lack of evidence in the literature on these outcomes.
Although weight loss is associated with a negative prognoses, illness is a major confounder. Studies are lacking on the causal relation between low BMI, weight loss and negative outcomes(7). Unfortunately, the report provides no implications for clinical practice.
In a reaction, the Dutch geriatricians argued that malnutrition in the elderly is almost always a result of a combination of diseases, which is better known as a 'geriatric syndrome'. Uncoupling malnutrition from disease is, according to these geriatricians, impossible. Their advice is to regard and treat malnutrition as a geriatric syndrome, having multiple causes and needing a multi-faceted treatment(8).
While most studies (including the ones in this thesis) have principally emphasized the nutritional intervention, we believe that future studies among elderly people should encompass a nutritional intervention in combination with interventions on the possible risk factors and causes.

Intervention
Patients were randomly allocated to either the intervention group or the control group. Patients in the intervention group received a multi-component nutritional intervention, consisting of a combination of energy, protein, vitamin D and calcium. In addition patients were counselled by a dietitian every second week. Patients in the control group received usual care. Nutritional support was only prescribed by their physician or dietitian. Generally it meant that no nutritional support was offered following discharge from the hospital. However, prior to inclusion in this study, some patients in the control

group were already using oral nutritional supplements or had consulted a dietitian. By excluding these patients from analyses it did strengthen our results.
In contrast to other studies, our study demonstrated an adherence rate to the nutritional intervention above 80%. This may explain the effects found, and the absence of these effects in other studies. Previous studies have shown adherence rates of approximately 50% for oral nutritional supplements(9;10). In a similar study, adherence was only 38% in the oral nutritional supplement group and 50% in the matched placebo group(11). Low adherence rates have also been reported for vitamin D supplementation. According to a meta-analysis, 21 of the 29 studies had an adherence rate of calcium (and vitamin D) supplementation of less than 80%(12).
In contrast to most other studies, patients in this study were counselled by a dietitian. The good adherence rate may be attributed to this extra counselling. This is supported in a recent review by Baldwin et al. (13). Rüfenacht et al.(14) published a study in which patients receiving nutritional intervention combined with dietetic counselling gained more weight compared with those without dietetic counselling.

Statistically significance was found in the nutritional intervention resulting in increased energy intake, protein intake and serum 25-hydroxy vitamin D levels in the intervention group. In contrast with some other studies, the nutritional intervention did increase the total nutritional intake instead of replacing the normal diet with nutritional supplements (15;16).
Our study was conducted using a relatively low dose of vitamin D (per day: 400 IU of calcium-vitamin D supplementation and 176 IU of oral nutritional supplements). After the start of this study in 2006, the advised dose of vitamin D supplementation by the Health Council of The Netherlands for elderly people increased to 800 IU/day(17). We hypothesize that a higher dose of vitamin D would further reduce the fall incidence. Additional research is recommended to study a dose-response design.

This study does not supply an answer as to which specific nutritional component, combination of components and/or counselling is responsible for the effects found. The chosen multi-component intervention could be recommended since malnutrition in these frail patients can be regarded as a geriatric syndrome, desiring a multi-factorial approach.

Costs
Cost-effective studies are receiving a lot of attention. However, there is very limited evidence of economic benefits of a nutritional intervention. Rypkema et al. concluded, in a controlled study, that there were no statistically significant differences in costs

between two different wards of geriatric patients(18). Quite recently Norman et al.(19) published a trial with a study design very similar to our study. They concluded that a three month intervention including oral nutritional supplements in the post-discharge setting increased quality of life in malnourished patients and that this was also cost-effective.

The number of studies based on post-discharge nutritional support and their cost-effectiveness is minimal. As far as we know there is only one study to date(20) that described the cost benefits, rather than the cost-effects. That study was unable to demonstrate economic benefits of post-discharge nutritional support. Seventy percent of the total costs incurred were due to hospital admission costs. This is in sharp contrast to our study in which only 20% was caused by hospital admission costs.

Elia et al. (21) concluded in a review article that the costs of malnutrition are even higher than the costs owing to obesity, and that the consequences of malnutrition are responsible for 10% of the health care budget. They concluded that minimal savings from a nutritional intervention could lead to substantial "absolute" cost savings in health care. For the Dutch situation, Freijer et al. calculated that the total extra costs of managing adult patients with disease related malnutrition was estimated to be € 1.9 billion in 2011 which equals 2.1% of the total Dutch national health expenditure (article in press)(22). We conclude that there is a lack of cost-effective studies of nutritional interventions and that our study is the first is this kind.

The results of our study demonstrate cost-effectiveness for functional limitations. In terms of cost-effectiveness it could be important to deduce which component or combination of components of the given nutritional intervention was responsible for the effect found. An important point to be made here is that the costs of vitamin D supplementation is much lower than counselling costs by a dietitian. Additionally, the (non significant) increase in health care costs were mainly attributed to the use of an expensive qualified university dietitian (150% more expensive than a dietitian in primary care). By shifting nutritional support following discharge to primary care, costs could be reduced. Also, hypothetically speaking, costs could be reduced by larger packages of oral nutritional supplements (e.g. 500/1000 ml each package) along with cheaper forms of distribution (e.g. supermarkets in stead of pharmaceutical service centres or pharmacies). Possibly, health care costs could be reduced by a nutritional intervention when studying the absenteeism among the younger working elderly population. Future research is recommended to address the above mentioned.

Outcomes

In this study we were unable to demonstrate statistically significant differences in quality of life, physical activities and hand grip strength. We presume that the order of effects would be firstly weight gain, then followed by improvement in physical activities, and finally improvement in quality of life. However, in conformity with earlier studies, we were unable to demonstrate effects on physical activities and quality of life in these old, frail, and ill patients following just three months of nutritional intervention. Therefore, we hypothesize that for such an intervention study to possibly have effects on other relevant end points a minimum duration of six months is required. Besides, it is possible that there was not enough power to demonstrate differences in these outcomes and the distribution within the outcomes was too high.

Predictive equations and survival

We concluded that resting energy expenditure prediction equations and fixed factors (kcal/kg/d) were inadequate for hospitalized malnourished elderly patients. Therefore, we suggest always to measure energy expenditure in this group of patients. However, measuring resting energy expenditure by indirect calorimetry is not very feasible in most clinical settings, due to time consuming measurements, lack of trained personnel, and the use of expensive equipment. Although not yet available, more effective and accurate, bedside equipment for measure resting energy expenditure would be more than welcome. A new resting energy expenditure prediction equation for malnourished elderly patients could be developed. However, there is a proliferation in the development of predictive equations, so we should be careful in developing another one and creating appearance accuracy. Meanwhile, we should inform colleagues in the field of work that resting energy expenditure predictive equations are not a reliable source in predicting energy needs in malnourished elderly patients. They are potentially too small foundation for establishing feasible dietary goals and need to be interpreted with care. We strongly advise colleagues to monitor ones body weight during nutritional intervention in daily practice.

In another group of patients, we could question ourselves whether or not it is beneficial to initiate dietary goals to improve nutritional status. Malnourished cognitively impaired patients, along with a medical diagnosis of malignancy and vascular disease seemed to die earlier following discharge than other patients. The question arises as to whether or not we should always offer intensive nutritional support to these patients, or perhaps it would be better to prioritize their needs differently. In other medical diagnosis nutritional support should carefully be re-considered in the light of perceived benefits and health care costs in individual patient circumstances.

Our study does not have enough scientific value to draw sound conclusions, however, it opens a door to discussion and lays the foundation for further research in this field. Developing tools which identify patients who have a higher probability of living longer or could benefit from nutritional intervention would be helpful. Future research, should systematically categorize patients with dementia and delirium as so many of these patients with either problem were probably not included in the study to date, and as one can expect those to be the healthiest group with cognitive problems.

Methods

From a meta-analysis published by the Cochrane Library 2009(23) and a systematic review by Cawood et al. (24) we can conclude that effectiveness of oral nutritional supplements has been proven in earlier studies. However, most studies had small sample sizes, poor quality and/or design. Milne et al.(23) described that only 19 of the 62 included studies in the meta-analyses were performed with sample sizes of 100 people or more. Also, only 19 of the studies were randomized controlled trials. Only 24 of the 62 studies were analysed according to the intention-to-threat principle. With this in mind, these results should be interpreted with caution. Authors indicated a lack of studies with outcomes other than body weight (e.g. quality of life, physical activities and functional limitations). Our study addresses a number of the described short comings mentioned above: intention-to-treat principle, sizable patient group, adequate randomization and relevant endpoints.

However, there were some limitations in the study design. Firstly, both patients and investigators were aware of the group assignment, due to the open study design. This limitation was partially adjusted by blinding the researcher during the analyses. However, socially desirable answers from patients could have biased the results. Therefore, a double blind controlled design would have been more preferable. Secondly, in our data, loss to follow-up accounted for 28%, probably as a result of the most ill patients with the worst nutritional status. On the one hand, results found could be underestimated due to the relatively healthy patients group. On the other hand, maybe no effect could be realized in the most ill patients because of their worse condition. Finally, we did not study mortality rates as an outcome measurement, but are planning to study this in the near future.

Comparison to literature

When designing our study, no earlier studies evaluating post-discharge nutritional intervention in malnourished elderly patients had been published to date. In December 2009, McMurdo et al.(11) published a study very similar to ours, but in comparison to our study they were unable to demonstrate statistically significant differences between

intervention and control patients. In their study, patients received oral nutritional supplements, but received no additional counselling by a dietitian. Also, the adherence was much lower (50%) compared to 80% in our study. We assume that combining oral nutritional supplements with additional dietetic counselling played an important role in the outcomes of our study.
Another study, by Edington et al.(20), concluded that in already malnourished elderly individuals, it may be too late to expect improvement of function, quality of life or to reduce health-care costs, simply by providing nutritional supplements following hospitalization. The nutritional support in their study lasted for 8 weeks with a followed-up period for 24 weeks. After the eight week nutritional intervention, they found improvement of body weight and hand grip strength in the intervention group. However, these results had diminished by the 24 weeks follow-up. We disagree with the authors that the nutritional intervention was not effective and hypothesize that individualized counselling is necessary to succeed nutritional intervention therapy and to improve outcome. Our results support this hypothesis as during active nutritional intervention we were able to demonstrate improved outcomes (in functional limitations and falls). Unfortunately, we have no follow-up data in our study after the 12 weeks of nutritional intervention.
Recently Feldblum et al.(25) published a randomized study on the effects of six months post-discharge nutritional support by a dietitian, in malnourished elderly patients. They concluded that patients in the intervention group had lower mortality rates and better nutritional status than patients in the control group. They were unable to demonstrate statistically significant differences in other outcomes (function, cognition, depression). In their study there was also a high drop-out rate (26%). The authors also hypothesize that these positive effects were possibly caused by the individualized nutritional intervention.

After having reviewed the literature, we conclude that the effectiveness of nutritional support on nutritional status (especially body weight) has been demonstrated by several studies to date. However, there is a lack of other, more relevant, outcome parameters, such as functional outcomes.
Additionally, since malnutrition is often related with somatic, psychological, functional and social problems, researchers agree that a nutritional intervention needs a multi-factorial approach, for example in combination with physical exercise. Recently, following a European consensus meeting on sarcopenia, the conclusion was drawn that physical interventions in elderly led to improved functional outcomes(26). Kortebein et al.(27) discussed that 10 days of bed rest contributes to functional decline. However, these studies mainly focussed on relatively healthy elderly in a normal nourished status.

Studies addressing both malnutrition and poor physical functioning have not yet been published.
Disturbance of the immune system is one of the causes of sarcopenia (28;29). Although the nutritional modulation of immune function has attracted much attention recently, predominantly by the use of immune-modulating agents, the presumed immune-stimulating role of 'regular' macronutrients and micronutrients has, in comparison, received only little attention. Since we found no improvement of immune markers by the applied nutritional intervention (focus on macro- and micronutrients) in our exploratory study, we may conclude that the improved outcomes probably were caused by patients' improved health status during time. Future research could focus on a combined therapy of oral nutritional supplements and physical exercise in a larger sample of relatively healthy, malnourished elderly.

Relevance and implications for public health and clinical practice

At this moment, organized post-discharge nutritional support is limited. However, in a diversity of forums this has not gone unnoticed. The Dutch General Practitioners Society has developed and published a primary care collaboration agreement, in which the responsibility of several disciplines on the approach of malnutrition is described(30). The Dutch Steering Group Malnutrition is focussing on early recognition and adequate treatment of malnourished people in all Dutch health care settings. Recently, clinical geriatricians have published a guide on malnutrition in geriatric patients(31), in which they also focus on post-discharge nutritional interventions in primary care.
However, all these post-discharge initiatives are still in early development. Here we would stress the importance of nutritional support in malnutrition in primary care because: 1) health care is shifting away from hospital towards primary care, 2) malnutrition develops frequently in primary care and will be treated there too (after treatment of the medical problem), 3) our population is aging, and 4) adequate treatment of malnutrition will help maintain or rehabilitate self-reliance of the (frail) elderly.
Evidence from well designed studies involving nutritional interventions are only slowly gaining ground. However, this should not delay or stop quality improvement of nutritional care.
There is growing evidence that malnourished elderly patients benefit from nutritional support. A small increase in quality of life could have large effects in this vulnerable

population. Besides, independent of proven effectiveness, it is unethical to withhold sufficient nutrition and drinks from patients.
Possibly, cost-effectiveness studies are less applicable in this old and frail group, as health care costs increase considerably in the final years of life(32).

For future research we would suggest a better construction for post-discharge nutritional care in geriatric patients. Studies should focus on standard post-discharge nutritional support accompanied by dietetic counselling. Newly developed specialized elderly welfare centres could play an important role in managing these elderly patients. Introducing standard screening on nutritional status in clinical and outpatient setting could possibly prevent patients from developing malnutrition. Nutritional interventions should be combined with physical activity and probably be given for a period of at least six months and follow-up should last even longer.

Conclusion

We conclude that three months post-discharge nutritional support in malnourished ill elderly patients decreases functional limitations, number of falls and increase body weight. Additionally, we demonstrated cost-effectiveness for functional limitations. We were unable to demonstrate statistically significant differences on quality of life, physical activities, hand grip strength and immune markers.
Finally, we also explored new research areas, such as the accuracy of predictive equations for malnourished elderly and the role of nutritional support in malnourished and cognitively impaired elderly patients.

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SUMMARY

Summary

Post-discharge nutritional support in malnourished ill elderly patients –
Effectiveness and cost-effectiveness

Introduction

This thesis describes the effectiveness and cost-effectiveness of post-discharge nutritional support in 210 malnourished elderly patients. Patients were randomized into an intervention group or a control group. Patients in the intervention group received an energy and protein enriched diet, oral nutritional supplements, calcium-vitamin D supplementation and were supported by dietetic counselling. Patients in the control group received usual care.

Patients were included on hospital admission and follow-up continued untill three months following hospital discharge. Primary outcome parameters were functional limitations and physical activities.

This summary presents the main findings from this study.

Summary of main findings

Effectiveness

Firstly, a three month duration multi-component nutritional intervention (energy and protein enriched diet, oral nutritional support, calcium-vitamin D supplementation supported by dietetic counselling) in malnourished patients resulted in an increase in body weight. This finding was statistically significant for patients in the highest body weight category, but not significant in those with lower body weights.

Secondly, a statistically significant decrease was found in functional limitations in the intervention group compared to the control group. Patients having received the nutritional intervention, for example, were able to climb up a stairs and/or dress and undress themselves, while patients in the control group could not. What is important about this finding is that most patients are less concerned about an increase in their body weight while a decrease in functional limitations can play an important role in their independence. No statistical significant differences between groups could be demonstrated for physical performance, physical activities, fat-free mass, and handgrip strength.

Thirdly, a statistical significant increase was found among patients in the intervention group on energy intake, protein intake and serum 25-hydroxy vitamin D compared to patients in the control group. A study on fall incidence demonstrated that the number of

patients who had experienced falls and the mean number of fall incidents considerably decreased in patients in the intervention group, compared to patients in the control group.
Finally, in an exploratory study on the effect of the nutritional intervention on a selection of immune parameters, no statistical significant differences between groups in immune markers, endocrine markers and a selection of micronutrients could be demonstrated. The better health status of the selected group of patients could have played a part in the results found.

Cost-effectiveness
Alongside a significant decrease in functional limitations we were able to demonstrate that the given nutritional intervention was cost neutral. Both groups spent approximately € 9000 on health related costs in the three months following discharge from the hospital. This study concludes that an investment of € 6500 was needed to create a 95 percent change to decrease functional limitations.
This study could not demonstrate cost-effectiveness for quality of life and physical activities.

Survival of malnourished cognitively impaired patients
In a sub-analysis survival was studied in malnourished elderly patients with cognitive impairment. Survival minimized among patients diagnosed with a malignancy or vascular disease in addition to their malnutrition and cognitive impairment.

Resting energy expenditure; predictive equations versus measurements
This final study describes the resting energy expenditure of malnourished elderly patients. Resting energy expenditure can be measured by indirect calorimetry. However, this method is hardly feasible in most clinical settings, due to time consuming measurements, lack of trained personnel and expensive equipment. In clinical practice, predictive equations to determine resting energy expenditure are used as an alternative to solve this problem. In this study 33 different equations were compared to the measured values. Predictions of resting energy expenditure for malnourished ill elderly patients during hospitalization were subject to significant errors. The best developed prediction equations, thus far, predicted only 40% of patients accurately. Three months following discharge was this increased to 66%.

Conclusion

In conclusion, the studies in this thesis demonstrated that three months nutritional intervention in malnourished elderly patients increases body weight, decreases functional limitations and decreases falls. No effectiveness could be demonstrated for hand grip strength, fat free mass, physical activities and physical performance.

Future studies could focus on standard post-discharge nutritional support accompanied by dietetic counselling. Newly developed specialized elderly welfare centres could play an important role in managing this kind of intervention. Promising possibilities are nutritional interventions combined with physical activity, especially when provided for a minimum period of six months.

SAMEN-VATTING

Samenvatting

Transmurale voedingszorg bij ondervoede zieke oudere patiënten –
Effectiviteit en kosteneffectiviteit

Inleiding

Dit proefschrift beschrijft de effectiviteit en kosteneffectiviteit van transmurale voedingszorg bij 210 ondervoede oudere patiënten. De patiënten werden gerandomiseerd in twee groepen waarbij de ene groep een energie- en eiwitverrijkt dieet, drinkvoeding, calcium-vitamine D suppletie en consulten door een diëtist kreeg aangeboden en de andere groep de gebruikelijk zorg kreeg.
Patiënten werden gevolgd van opname in het ziekenhuis tot en met drie maanden na ontslag. De belangrijkste uitkomstmaten van de studie waren functionele beperkingen en lichamelijke activiteit.
Deze samenvatting is een korte weergave van de belangrijkste bevindingen

Effectiviteit

Het geven van een drie maanden durende voedingsinterventie (bestaande uit een energie- en eiwitverrijkt dieet, drinkvoeding, calcium-vitamine D suppletie en consulten door een diëtist) aan ondervoede ouderen, leidde tot gewichtstoename. De gevonden verschillen waren significant voor patiënten met het hoogste lichaamsgewicht categorie, maar niet significant voor patiënten in de laagste lichaamsgewichtcategorie.
Daarnaast nam het aantal functionele beperkingen significant af bij patiënten in de interventiegroep. Zij konden na de gegeven interventie bijvoorbeeld zelfstandig een trap op- en aflopen en zichzelf aan- en uitkleden, terwijl patiënten in de controlegroep dit niet konden. Deze bevinding is belangrijk, omdat de toename van het lichaamsgewicht voor de meeste mensen niet zo veel betekent, terwijl een afname in functionele beperkingen van groot belang kan zijn voor hun zelfstandigheid.
Voor de mate van lichamelijke activiteit, lichamelijke prestatie, vetvrije massa en handknijpkracht hebben wij geen verschillen kunnen aantonen tussen de twee onderzoeksgroepen.
Patiënten in de interventiegroep hadden na de interventie een significant hogere energie- en eiwitinname en een significant hogere serum vitamine D spiegel dan patiënten in de controlegroep. Een studie naar valincidentie liet zien dat het aantal patiënten dat viel en het gemiddeld aantal valincidenten aanzienlijk lager was in de interventiegroep.

In een exploratieve studie naar het effect van de gegeven voedingsinterventie op een selectie van immuunmarkers, endocriene markers en micronutriënten, konden geen significante verschillen aangetoond worden tussen de twee onderzoeksgroepen. De betere gezondheid van deze geselecteerde groep patiënten speelde hierin mogelijk een rol.

Kosteneffectiviteit
Naast een significante afname van functionele beperkingen, heeft deze studie aangetoond dat de gegeven voedingsinterventie koste neutraal is voor functionele beperkingen. Beide onderzoeksgroepen maken ongeveer € 9000 aan gezondheid gerelateerde kosten in de drie maanden na hun ontslag uit het ziekenhuis. Deze studie concludeert dat een investering van € 6500 nodig was om een 95 procent kans te hebben om te verbeteren in functionele beperkingen.
In deze studie kon geen kosteneffectiviteit worden aangetoond voor kwaliteit van leven en lichamelijke activiteit.

Overleving van ondervoede patiënten met een cognitieve beperking.
In een subanalyse is bij ondervoede oudere patiënten met een cognitieve beperking de overlevingsduur onderzocht. Wanneer patiënten naast ondervoeding en een cognitieve beperking tevens een medische diagnose van vasculaire aandoening of maligniteit hadden, bleek de overlevingsduur zeer gering.

Rustmetabolisme; formules versus meten
De laatste studie onderzocht het rustmetabolisme van ondervoede ouderen. Het rustmetabolisme kan gemeten worden met behulp van indirecte calorimetrie. Maar omdat deze methode veel tijd kost, duur is en er veel training nodig is voor diegene die de meting uitvoert, wordt er in de praktijk veelvuldig gebruikt gemaakt van formules die het rustmetabolisme benaderen. In deze studie werden 33 verschillende formules vergeleken met het gemeten rustmetabolisme bij ondervoede ouderen. Geconcludeerd kan worden dat de formules grote afwijkingen vertonen ten opzichte van de gemeten waarden wanneer deze toegepast worden bij ondervoede ouderen. De beste formule schat het energieverbruik bij ongeveer 40% van de patiënten correct in. Drie maanden na ontslag uit het ziekenhuis is dat 60%.

Conclusie

Concluderend tonen de studies binnen dit proefschrift aan dat het geven van een drie maanden durende voedingsinterventie aan ondervoede oudere patiënten leidt tot een toename in gewicht, een afname in functionele beperkingen en een afname in vallen. Er kon geen effectiviteit worden aangetoond voor handknijpkracht, spiermassa, lichamelijke activiteit en lichamelijke prestatie.

Toekomstige studies zouden zich kunnen richten op het standaard aanbieden van transmurale voedingszorg, ondersteund door een diëtist. Nieuw te ontwikkelen consultatiebureaus voor ouderen kunnen een belangrijke rol gaan spelen in de zorg voor deze alsmaar groter wordende groep ouderen. Mogelijk veelbelovend zijn voedingsinterventies gecombineerd met lichamelijke activiteit, zeker wanneer deze gegeven worden voor een periode van minimaal zes maanden.

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Dankwoord

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ABOUT THE AUTHOR

About the author

Floor Neelemaat was born on the 25th of April 1978 in Purmerend, The Netherlands.
After finishing secondary school at the Jan van Egmond College in Purmerend, she studied Nutrition and Dietetics at the University of Applied Sciences (HvA, Amsterdam) from 1996-2000, and received her Bachelor of Science degree. Subsequently she studied Human Nutrition and Epidemiology at the Wageningen University and Research centre (WUR, Wageningen) from 2000-2002, and received her Master of Science degree.
In 2003 she was employed at the VU University Medical Center (VUmc, Amsterdam) as a dietitian at the department of surgery. From 2004-2005 she studied the prevalence of malnutrition in the outpatient departments of the VUmc. In 2006, she started her PhD study on effectiveness and cost-effectiveness of post-discharge nutritional support in malnourished ill elderly patients. During the project she took methodological and statistical courses in the Postgraduate Epidemiology Programs of the EMGO Institute for Health and Care Research.
On occasion she teaches nutrition-related courses at the VU University, Amsterdam.

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