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Short-term individual nutritional care as part of routine clinical setting improves outcome and quality of life in malnourished medical patients

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Zusammenfassung

Zielstellung: Maßnahmen zur Behandlung krankheitsbezogener Mangelernährung sind selten und wenig praktikabel. In dieser Studie wird untersucht inwiefern die Energie- und Proteinaufnahme von Patienten mit Mangelernährungsrisiko durch eine individuelle Ernährungsbetreuung gesteigert werden kann und sich dies auf klinische Parameter und die Lebensqualität auswirkt.

Methoden: Eine randomisierte kontrollierte Interventionsstudie wurde durchgeführt. Risikopatienten, definiert mittels "Nutritional Risk Screening 2002", erhielten entweder eine individualisierte Ernährungstherapie (Interventionsgruppe) oder die Standardbetreuung (Kontrollgruppe). Ein engmaschiger Algorithmus wurde angewandt, um den täglichen individuellen Bedarf an Energie und Protein zu decken. Der Ernährungsstatus, das Körpergewicht und Serum-Vitaminkonzentrationen wurden bestimmt. Die Lebensqualität wurde mittels SF-36-Fragebogen erfasst sowie Komplikationen und die Wiedereintrittsrate registriert.

Ergebnisse: Die Ernährungsinterventionen führten zu höheren Aufnahmen (Mittelwert (Standardabweichung)) an Energie (1553 (341) kcal vs. 1115 (381) kcal, $p<0.001$) und Protein (65.4 (16.4) g vs. 43.9 (17.2) g, $p<0.001$). Die AONVA mit Messwiederholung ergab einen hochsignifikanten Interventionseffekt auf Protein- und Energieaufnahme. Interventionspatienten behielten im Vergleich zur Kontrollgruppe ihr Körpergewicht (0.0 (2.9) kg vs. -1.4 (3.2) kg, $p=0.008$). Positive Effekte auf Serum-Vitamin C-Konzentration (46.7 (26.7) μmol/l vs. 34.1 (24.2) μmol/l, $p=0.010$), SF-36 Summenfunktionsskala (37 (11) % vs. 32 (9) %, $p=0.030$), Anzahl an Komplikationen (4/66 vs. 13/66, $p=0.035$), Anzahl Antibiotikatherapien (1/66 vs. 8/66, $p=0.033$) und Wiedereintrittsraten (17/64 vs. 28/61, $p=0.027$) wurden ermittelt. Kein Unterschied trat bei Austritts-Körpergewicht, Hospitalisationsdauer und Mortalität auf.

Schlussfolgerung: Mangelernährte Patienten profitieren hinsichtlich ihres Ernährungsstatus, der Funktionalität und der Lebensqualität von einer Ernährungstherapie. Sie bekommen weniger Komplikationen, benötigen weniger Antibiotika-Therapien und werden seltener rehospitalisiert.

Abstract

Rationale: Nutritional strategies to treat malnutrition are rare and lack practicability in the hospital setting. This study aims at providing nutritional risk patients with individual nutrition care in order to raise energy and protein intake and investigate nutritional and clinical outcome parameters.

Methods: A randomized controlled intervention study was conducted. Risk patients defined by Nutritional Risk Screening 2002 were either randomised to individualised nutritional support (intervention group) or standard hospital care (control group). A tight algorithm was applied to meet daily individual requirements of energy and protein. The nutritional status, body weight and serum vitamin levels were determined. Quality of life was assessed (SF-36 questionnaire) and complications and readmission rates recorded.

Results: The nutritional interventions led to higher intakes (mean (standard deviation)) in energy (1553 (341) kcal vs. 1115 (381) kcal, $p<0.001$) and protein (65.4 (16.4) g vs. 43.9 (17.2) g, $p<0.001$). Repeated measure AONVA revealed a highly significant effect on protein and energy intake. Intervention patients kept their body weight in comparison to control patients (0.0 (2.9) kg vs. -1.4 (3.2) kg, $p=0.008$). Positive effects on serum ascorbic acid level (46.7 (26.7) μmol/l vs. 34.1 (24.2) μmol/l, $p=0.010$), SF-36 function summary scale (37 (11) % vs. 32 (9) %, $p=0.030$), number of complications (4/66 vs. 13/66, $p=0.035$), antibiotics therapy (1/66 vs. 8/66, $p=0.033$) and readmissions (17/64 vs. 28/61, $p=0.027$) were recorded. No differences in discharge body weight, length of stay and mortality were found.

Conclusions: Malnourished patients profit in terms of their nutritional status, functionality and quality of life from nutritional support. They gain fewer complications, need fewer antibiotics and are less often rehospitalised.

Preface

Does malnutrition matter? Globally, malnutrition is still the number one health risk responsible for disease and death. The most recent estimate of the Food and Agriculture Organisation (FAO) from October 2010 says that 925 billion people are undernourished, i.e. 13 % of the world population [1]. The vast majority of them live in developing countries, i.e. sub-Saharan Africa and Asia, and children are especially affected. It is due to chronic food deficits of various reasons, that energy, protein and micronutrient deficiencies are widely spread. As Africa is far away, most people reduce hunger and starvation to this continent. However, the FAO report also shows that about 19 billion people suffer from hunger in developed countries [1]. Since a lack of food as reason for undernutrition is unlikely in an economically successful region that leaves the obvious question: How did this come about then?

Historical research revealed that as late as the early 19^{th} century poverty and chronic hunger dominated in many parts all over Europe [2]. According to the first epidemiological data of today's French region Alsace, a malnutrition prevalence of 16 % was recorded especially among the non-privileged population like tailors, fishermen and the unemployed [3]. Criteria to define malnutrition were mainly clinical signs of single micronutrient deficiencies. Until the middle of the 20^{th} century food supplies became adequate and primary malnutrition declined to a minimum after the Second World War in Europe [4]. In Switzerland, post-war investigations initiated by governmental institutions revealed an impaired micronutrient status in people living isolated up in the mountains. However, the total energy intake was sufficient [5]. A suboptimal diet related to a change from self-supply to dependence on foreign products and "an erroneously assumption that a nutrition rich in proteins is complete already", was considered as reason. In an intervention trial in 1957, children were provided with ground nuts (source of thiamine) and one of the first Swiss functional foods (a multivitamin Ovomaltine® bar) additionally to the normal food. In comparison to earlier data of the same population, the study showed a reduction of single nutrient deficiencies resulting in less school absences due to illness [6]. Since post-war time the further development of food supply, storage and trade widely led to the disappearance of macro- and micronutrient deficiencies due to lack of food. In contrast, overnutrition dominates with an epidemic extent in present generations [7]. However, further economic and social developments brought back historic reasons for malnutrition in certain situations. The consumption of cheap, processed and low nutrient food may lead to partial undernutrition today, especially in low-income families or alcohol/drug addicts [8, 9, 10].

A secondary form of malnutrition has increasingly been recognised in our aging society and recently occupied politics [11]. Many elderly have difficulties with food supply due to age-related handicaps, illness and loneliness thus suffering malnutrition [12]. Besides,

care institutions struggle with exorbitant high numbers of malnutrition among residents [13, 14]. Although the majority of malnourished people live at home, malnutrition is especially precarious in acute disease situations, i.e. when hospitalised [15]. Then, the disease itself and its treatment influence food intake [16]. Additionally, hospitalised patients put themselves in the care of physicians and nursing staff. It is reasonable to suppose that one of the most basic needs - eating - is fulfilled. However, the situation is different, attributing nutrition and food intake a minor role in comparison to diagnostic and treatment options during hospital routine [17]. The necessary basis for convalescence, health and last but not least life is then missing [18].

In this thesis the current state of knowledge on secondary, disease-related malnutrition is outlined. The development of a nutritional strategy that can be easily implemented in the clinical setting was of major interest. As the main practical part, this nutritional strategy was applied and evaluated in a randomised controlled intervention trial which was performed at Kantonsspital Liestal/Switzerland from January to November 2007. Great importance was attached to the planning of the study and the homogenous performance of interventions as (mal)nutrition studies often lack statistical quality [19]. Once the first patient was included in the study, busy and demanding eleven months of malnutrition screening and treatment started. Patient recruitment, nutritional interventions and data collection - everything went incredible well. Six months of follow-up went along with the main intervention study until june 2008 and data analysis started. The results of this analysis finally objectively verify the subjective personal experiences during the study time. They show the high potential of an adequate food intake during acute diseases. Patients do eat sufficiently if food is adequately supplied and thus preserve body weight and a better physical function. Additionally, the higher intake of energy and protein lead to fewer complications, less antibiotics to treat hospital-acquired infections and fewer readmissions. A person additional to the ward staff and educated in nutrition may hence be beneficial for hospital patient care.

In summary, speaking about undernourished people in the developed world still means speaking about a minority. However, the circumstances leading to malnutrition and the impact for the individual and society are important. Malnutrition is about to reach the same high health care costs which are attributed to adiposity/obesity. But in contrast, malnutrition strategies are rarely implemented [20, 21]. Although nutritional studies are difficult to perform, nutritionists are encouraged to perform more demanding but rewarding randomised controlled intervention nutrition trials in order to collect convincing evidence. By this work the author wants to point to the unfavourable hospital routine regarding nutritional care and hopes to support the process of finding solutions for a better nutrition in hospitals.

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List of abbreviations

25-OH-D_3	25-Hydroxy-Cholecalciferol (25-OH-Vitamin D_3)
ADL	Activities of daily living
AIDS	Aquired immunodeficiency virus
ANOVA	Analysis of Variance
BIA	Bioelectric Impedance Analysis
BMI	Body Mass Index
CG	Control group
CKK	Cholecystokinin
COPD	Chonic Obstructive Pulmonary Disease
ELISA	Enzyme-linked immunosorbent assay
EORTC	The European Organisation of Research and Treatment of Cancer
ESPEN	The European Society for Clinical Nutrition and Metabolism
FAO	Food and Agriculture Organisation
FFM	Fat free mass
HIV	Human Insufficiency Virus
HPLC	High performance liquid chromatography
I.C.	Informed Consent
ICD-10	International Classification of Diseases and Related Health Problems (10th edition)
ICU	Intensive Care Unit
IG	Intervention group
ITT	Intention-To-Treat
I.U.	International Units
LMF	Lipid-mobilising factor
LOS	Length of stay
LOS_e	LOS from study inclusion to possible ward discharge
LOS_f	LOS from study inclusion to definite ward discharge
LOS_g	LOS from ward admission to possible ward discharge
LOS_h	LOS from ward admission to definite ward discharge
LOS_i	Hospital LOS
MNA	Mini Nutritional Assessment
MUAC	Mid upper arm circumference
NRS-2002	Nutritional Risk Screening 2002
ONS	Oral nutritional supplements
PAL	Physical activity level
PEM	Protein-Energy-Malnutrition

PG-SGA	Patient-generated Subjective Global Assessment
PIF	Proteolysis-inducing factor
PP	Per-Protocol
REE	Resting Energy Expenditure
SF	Stress (disease) factor
SF-36	Short form 36 questions questionnaire of quality of life
SF-PF	SF-36 subscale Physical Function
SF-GH	SF-36 subscale General Health
SF-RP	SF-36 subscale Role Physical
SF-BP	SF-36 subscale Bodily Pain
SF-SF	SF-36 subscale Social Function
SF-RE	SF-36 subscale Role emotional
SF-MH	SF-36 subscale Mental Health
SF-VT	SF-36 subscale Vitality
SF-PCS	SF-36 summary scale Physical Component Summary
SF-MCS	SF-36 summary scale Mental Component Summary
SGA	Subjective Global Assessment
SPSS	Statistical Package for the Social Sciences
TEE	Total Energy Expenditure
TNF-α	Tumor Necrosis Factor α
UK	United Kingdom
UV	Ultraviolett
QoL	Quality of life

1 Theoretical background

1.1 Definition and prevalence of disease-related malnutrition

Disease-related malnutrition is not new [22]. However, empiric data describing the nutritional status of hospitalised patients has been only available since the late 20th century. According to that, between 20 % and 50 % of all patients are malnourished [23, 24, 25, 26]. The first multi-centre cross-sectional study in German hospitals showed that every fourth adult patient is malnourished at admission or has a risk of becoming malnourished during hospital stay [27]. Prevalence rates thereby depend on hospital departments and vary from 8 % in gynaecologic patients to 56 % in geriatric patients. However, prevalence varies even within specialities and appears to depend on numerous options of diagnosing malnutrition (see table 1.1). Besides, an inconsistent definition of malnutrition is applied even in current guidelines [28, 29, 30].

Table 1.1: In-hospital malnutrition prevalence

Population	Screening tool	Prevalence (%)	Reference (Year)
Multidisciplinary	NRS-2002[1]	32.6	Sœrensen et al. (2008) [31]
General medicine	PG-SGA[2]	53.0	Thomas et al. (2007) [32]
General medicine and surgery	SGA	39.0	Kyle et al. (2006) [33]
General medicine and surgery	NRS-2002	28.0	Kyle et al. (2006) [33]
Multidisciplinary	SGA	27.4	Pirlich et al. (2006) [27]
Oncology	SGA	37.6	Pirlich et al. (2006) [27]
Geriatrics	SGA	56.2	Pirlich et al. (2006) [27]
Geriatrics	NRS-2002	40.3	Bauer et al. (2005) [34]
Geriatrics	SGA	45.0	Bauer et al. (2005) [34]
Oncology	PG-SGA	52.0	Segura et al. (2005) [35]
General medicine and surgery	NRS-2002	39.9	Rasmussen et al. (2004) [36]
Multidisciplinary	NRS-2002	22.0	Kondrup et al. (2002) [37]
General medicine	NRS-2002	24.8	Kondrup et al. (2002) [37]

[1] Nutritional Risk Screening 2002

[2] Patient-generated Subjective Global Assessment

Only recently an aetiology-based definition of disease-related malnutrition has been published [38]. Three conditions which combine various degrees of under- or overnutrition and inflammation (acute or chronic) are denominated. Hence, malnutrition is divided into "starvation-related malnutrition" (no inflammation but starvation like in anorexia nervosa); "chronic disease-related malnutrition" (mild or moderate chronic inflammation like in cancer) and "acute disease/injury-related malnutrition" (severe inflammation like in burns or trauma). In the latter two, food intake may or may not be comprised but nutrient requirement is impaired. Additionally, as defined by The European Society for Clinical Nutrition and Metabolism (ESPEN), a "severe nutrition risk" can lead to the manifested status and determines outcome especially if inflammation and a reduced food intake are concurrent disorders [30].

In this work "malnutrition" is used shortened for the above mentioned term "chronic disease-related malnutrition". As the main focus is placed on macronutrient intake, malnutrition in this context includes the hitherto favoured term "protein-energy malnutrition (PEM)" as well. However, this term is imprecise since it is often accompanied by micronutrient deficiencies, does not take the inflammatory component of disease into account and so far has been rather used to described undernutrition. A nutritional risk leading to disease-related malnutrition as mentioned above is referred to as such in the text.

1.2 The underlying causes of disease-related malnutrition

The pathogenesis of malnutrition is multifactorial and underlying causes are often interwoven. Apparently, a persistent imbalance between (a decreased) nutrient intake and (increased) nutrient requirements causes a decline in nutritional status.

1.2.1 Conditions with insufficient nutrient intake

Disease in general is often associated with an impaired nutrient intake [12, 39, 40]. In particular cancer patients suffer from anorexia or considerable reduction of appetite [41, 42, 43]. Early satiety typically accompanies tumors of the upper gastrointestinal tract [44] and advanced stage liver disease (due to hepatomegaly and ascites [45, 46]). Neurological damage (e.g. stroke) and dysphagia because of mechanical barriers (e.g. oesophageal tumours) often require artificial nutrition in order to fully cover nutrient requirements [47, 48]. Taste and odour abnormalities occur during and after tumour therapy, i.e. chemotherapy, radiation or surgery [49, 50, 51]. Congestive heart failure and pulmonary diseases are often accompanied by an impaired exercise capacity. Hence, dyspnoe and physical exhaustion lead to unfinished meals [52, 39, 53]. Especially in geriatric patients functional limitations (e.g. uncomfortable or missing dentures and reduced saliva) contribute to malnutrition [54, 55, 56]. Besides, the elderly may need assistance to overcome handicaps with cutlery [57, 58]. Both depression, severe dementia and pain reduce food intake considerably [59, 60]. Vice versa, anorexia can also lead to depression [61]. In contrast, antidepressants and analgesia, especially opiods, also cause nausea and

emesis supporting the shortage of nutrients [62, 63, 64]. An unfamiliar environment, anxiety and loneliness reduce food intake [12, 53, 65]. In contrast, having lunch in company and an appealing dish with a range of food that can be chosen individually may increase food intake [66, 67, 68].

1.2.2 Insufficient nutrient intake during hospitalisation

Especially during hospitalisation various factors induce a decline in nutritional status [37, 69, 70]. In risk patients a rising energy deficit and an ongoing weight loss is reported during hospitalisation [71, 72]. Polypharmacy and disease treatment may lead to iatrogenic malnutrition [27, 73]. An insufficient malnutrition treatment algorithm resulting from a lack of responsibility [74, 75], unawareness among nursing staff [37, 76, 77] and simply the shortage of nursing staff [17, 58] results in delayed or inadequate nutritional support. Economic pressures lead to a maximum utilisation of expensive high-tech medical devices and hence crowded waiting lists, long waiting times and meal absences. Additionally, nil-by-mouth periods owing to the preparation for an investigation/treatment (e.g. surgery, colonoscopy) accumulate during a patient's journey especially if the patient is treated frequently [78].

1.2.3 Conditions with increased nutrient demands

Higher nutrient intakes may be demanded if digestion and absorption are impaired. In acute inflammatory bowel diseases, radiation induced enteritis and after intestine surgery the absorption capacity may be reduced and higher losses must therefore be compensated [79, 80]. Higher energy needs due to increased energy expenditures have been described with advanced renal insufficiency or Human Immunodeficiency Virus (HIV) [81, 82]. Moreover, there are patients with normal or even decreased energy expenditures requiring an individually targeted nutrition. For example in elderly patients with pressure ulcers resting energy expenditure (REE) was not higher than in patients without pressure ulcers [83]. In contrast, REE in patients with quadriplegia increased significantly in case of pressure sores [84]. Wide variations in total energy expenditure (TEE) were described in a study with underweight home-living chronic obstructive pulmonary disease (COPD) patients [85]. Cancer patients show an ambivalent REE alteration which is possibly related to the tumor stage and to the duration of the disease [86, 87]. While one third may have increased REE, another third has decreased or physiological REE [88, 89]. In liver cirrhosis, estimating REE is not at all successful and measurement by indirect calorimetry should be preferred [90]. Additionally, diet induced thermogenesis varies between 0.8 to 22 % [91]. A reduced food intake might thus further influence TEE. Critically ill patients might have increased requirements because of accelerated depletion during a hypermetabolic and inflammatory response (e.g. in trauma, burns or acute severe pancreatitis) [92, 93]. However, the concept of hypermetabolism shall be dealt with care as overnutrition can worsen the outcome, especially during the initial phase of critical illness [94, 95, 96].

1.2.4 Molecular basis for the causes of disease-related malnutrition

Inflammation and disease-triggered catabolic conditions make the nutritional status worse and limit the success of nutritional support at the same time [88, 97]. Especially skeletal muscle is rapidly lost during the acute host response accompanying the increased resting energy expenditure and the accelerated protein turn over [98]. Indicators of an impaired immune function dominate in malnourished patients. Thereby, the inflammatory response is extended and the synthesis of its components is reduced [99, 100]. The molecular basis for changes of the nutrient intake and the requirements during this metabolic response are only rudimentarily explored. A different neuroendocrine and humoral response of the sick organism promotes catabolic processes [101]. Especially determining in the sick metabolism can the increased action of inflammatory cytokines (TNF-α, interleukins 1 β, 6 and 8), eicosanoids, reactive oxygen species and catabolic enzymes (caspases, ubiquitin-proteasomes) be [102, 103]. Additionally, the imbalance of peripheral orexigenic (e.g. ghrelin, neuropetptid Y) and anorexigenic mediators (e.g. leptin, CKK) leads to insufficient food intake [104, 105]. For example, elderly people have a decreased ability to adapt their energy expenditure to a negative energy balance [106]. Especially the metabolism of cancer patients is further altered by factors produced by the tumor, e.g the Proteolysis-inducing factor (PIF) or the Lipid-mobilising factor (LMF) [107]. How these molecular changes influence the clinical picture and the pathogenesis of malnutrition in humans is a question of further research.

1.3 Clinical and financial implications of disease-related malnutrition

In the following section the focus is on the consequences of malnutrition on clinical parameters, for disease treatment and the economical impact on society. Meanwhile, there is ample evidence that an insufficient nutritional status limits a positive clinical as well as economical outcome. For example malnourished patients lose body weight more often and to a larger extent than their well-nourished counterparts [72]. A decreased appetite has been found to predict body weight loss [108]. An altered body composition, for example the depletion of fat-free mass, reduces functionality due to a decrease of both functional and supportive muscle tissue [109, 110]. Restrictions in activities of daily living (ADL), hand grip strength but also lung capacity have been reported for malnourished geriatric, stroke or COPD patients [111, 112, 113]. In comparison to well-nourished patients, the malnourished generally show a worse adherence to therapies. Cancer patients interrupt a chemo- or radiotherapy more often and struggle with more side effects in case of a nutritional risk [114]. In malnourished surgical patients wound healing is impaired [115]. Also, recovering time in patients with femur fracture is prolonged when several nutritional deficiencies are present [116]. Liver transplanted patients are more often and longer hospitalised in intensive care units (ICU) when malnourished according to Subjective Global Assessment (SGA) [117, 118]. Malnutrition significantly influences the ability to resist against infectious complications [119]. Mal-

nutrition defined by the Nutritional Risk Index, SGA or anthropometric parameters was associated with a higher occurrence of in-hospital acquired complications in general internal and surgery patients [120, 121, 122]. Moreover, the complication incidence was higher in geriatric patients and patients after liver transplantation in case of malnutrition determined by the Mini Nutritional Assessment (MNA) or by a combination of anthropometric parameters [123, 109]. In contrast, perioperativ nutritional support can prevented complications in malign surgery patients [124].

Measurements of quality of life by general questionnaires, e.g. the Short-Form quality of life questionnaire (SF-36), or specific questionnaires, e.g. the EORTC-questionnaire from the European Organisation for Research and Treatment of Cancer, revealed a decrease in both the physical and mental quality of life (QoL) when malnourished [125, 126, 127]. Malnutrition identified by SGA was related to poorer subjective QoL in a haemodialysis population [128]. The same applied to elderly patients of a nursing home with a low Body Mass Index (BMI) [129].

Numerous studies report that malnourished patients stay longer in hospitals depending on the extent of malnutrition [26, 27, 130]. Surgical and internal patients suffering from weight loss during hospitalisation were found to be readmitted more often [131, 132, 29]. Also malnourished outpatients as indicated by BMI were more often hospitalised [133]. Because of these adverse effects, malnourished survivors increase average treatment costs approximately threefold [121, 20]. In contrast, nutritional support was found to be cost-effective [134, 135]. According to a Dutch investigation an investment of 76 € per day (i.e. about one fifth of the daily costs) was sufficient to decrease hospitalisation by one day [136]. Malnourished patients have increased mortality compared to well-nourished patients in both the ambulant as well as the hospital setting [18, 133]. Cardiac patients' survival rate was lower when being cachectic [137]. In severely ill patients ICU mortality was higher in case of malnutrition [138, 139]. A recent Europe-wide study reported that among 5,000 patients 12 % of malnutrition risk-patients (i.e. NRS-2002$\geq$3) died in contrast to only 1 % of non-risk patients [31]. These numbers were similar in a Brazilian study that applied the SGA [121].

1.4 Options to diagnose disease-related malnutrition

In order to address the impact of malnutrition described in the previous section, there is need for a clear description and diagnosis. Several plasma parameters like serum albumin or lymphocyte count were discussed to describe the nutritional status [140, 141]. However, those parameters are influenced by the acute disease overlying the effect an impaired nutritional status would have [142]. In fact, serum albumin was found to be a strong predictor of morbidity and general mortality in hospitalised patients but not a nutritional marker [143, 144, 145].

A number of anthropometric parameters like body weight, BMI or the Mid Upper Arm Circumference (MUAC) have been found to be unreliable to define malnutrition [27, 29]. However, an (unintended) change in body weight, i.e. body weight loss, has prognostic value and thus is considered in most malnutrition screening tools [37]. A

body weight loss of 6 % in six months has been associated with a worse survival rate in patients with heart insufficiency [146]. Similarly, an altered body composition has been shown to predict malnutrition. In elderly, cancer and surgical patients the phase angle of Bioelectric Impedance Analysis (BIA) measurements and the amount of fat-free mass (FFM) is associated with the nutritional status [147, 148, 149]. Moreover, the phase angle predicts mortality [150, 151, 152]. Also, functionality measured by hand grip strength has prognostic relevance [153]. The latter methods are, however, not routinely applied at present and still reserved to study settings even though hand grip strength, for example, can be measured easily [154].

A more practicable option to detect malnutrition is a routine screening followed by a detailed nutritional assessment in risk patients. Meanwhile, various screening tools are available, but only a few are accepted for the clinical setting, e.g. Nutritional Risk Screening 2002 (NRS-2002 [155]), Subjective Gloval Assessment (SGA [156]) or Mini Nutritional Assessment (MNA [157]). These tools are time-saving because they rely on easily available parameters like body weight, height, eating habits, clinical signs etc. The NRS-2002 is recommended for hospitalised patients. It is based on a retrospective analysis of nutrition intervention studies. In comparison to other screening tools the NRS-2002 shows good concordance [158, 159, 160]. Specificity reaches 93 % whereas sensitivity is about 62 %, however, experience is needed to overcome high inter-examiner variability [155, 33]. In the pre-screening patients are classified according to the presence of a low BMI, body weight loss, reduced food intake and critical illness. The main screening follows only in case one pre-screening parameter indicates malnutrition (for details refer to A.1). Thereby a score is allocated, depending on the degree of nutritional impairment (body weight loss, reduced BMI and food intake) and the severity of disease (dimension of metabolic stress). Additionally, age is taken into account as a risk factor (one point added for patients equal or above 70 years). Hence, malnourished and at-risk patients are identified as soon as the score totals 3. The tool developers investigated whether the tool was able to select patients who profit from nutritional support (s. discussion). This issue will also be addressed in chapters 3 and 4.

1.5 Nutritional support for disease-related malnutrition

As described so far, malnutrition has detrimental effects but can be defined easily. Thus, treatment is important to overcome the adverse effects. However, the integration of individual nutritional care in the daily hospital routine is a challenging task [161, 162, 163]. A second challenge is the missing evaluation of nutritional support and the individual food intake [164, 165, 166]. It was shown in surgical patients that recent food intake is more important for wound healing than nutritional status defined by recent weight loss [167]. Even so, several investigations show that large amounts of food are wasted. At the same time, patients' nutrient intake is insufficient during hospitalisation [168, 169, 170]. Nevertheless, food intake can be increased as the following sections show.

1.5.1 Improving food intake by factors related to nutrition and food

Dietary counselling and timing of nutritional support

The nutritional intake may be improved by dietary advice provided by dieticians or nutritionists. Evidence, however, is insufficient or of poor quality as information about the counsellor and content of the advice is mostly missing [171]. Dietary advice is often compared to supplement intake being inferior or equally efficient in increasing the energy intake [172, 171, 173]. However, in cancer outpatients dietary advice given during radiotherapy was the only sustainable option to increase the energy and protein intake until three months after radiotherapy [114, 174]. Even survival rate and long-term QoL were improved by the dietary counselling in contrast to supplement or ad libitum intake [175]. Likewise, both dietary advice and supplement intake led to higher energy and protein intakes during hospitalisation, whereas only the advice had a sustained effect two months after discharge [176].

It is especially important to avoid a delay in nutritional support since the highest impact is expected at the beginning of hospitalisation. This is, however, not the current practice because a definition of patients who should receive nutritional support is often missing [177, 178]. One study showed that during hospitalisation malnourished patients lose more body weight, whereas nutritional support can reverse the body weight loss [72]. A meta-analysis of early versus delayed nutritional support in ICU revealed a benefit regarding infectious complications when patients received early nutrition [179]. Additionally, delayed nutritional support led to an irreversible cumulative energy deficit which was associated with death [180], whereas early nutritional support prevented a deficit and favoured survival in ICU patients [71].

In-between meals and food fortification

Natural energy-dense ingredients like cream, cheese or margarine increased the spontaneous energy intake in nursing home residents [181]. In comparison to a pre-test evaluation, a 36 % increase in energy intake (i.e. 504 kcal/d) was observed. A reduced portion size and meal fortifications with butter, cream, cheese and glucose powder resulted in a 286 kcal/day increase in energy intake in geriatric patients. The protein intake, in contrast, was unchanged [182]. Meals fortified with double cream and skimmed milk powder and supplementary in-between snacks such as cake or cheese sandwiches resulted in an increased energy intake of 255 kcal/day. In contrast, the protein intake was again unchanged [183]. Although natural ingredients are cheap options to raise the energy intake, the lack of additional protein and micronutrients may be important as the main increase was achieved by a higher intake of fat in the cited studies.

Oral nutritional supplements

Energy-dense multinutrient supplements (oral nutritional supplements, ONS) may be offered to patients who prefer drinking their calories [182, 184, 185]. According to a recent Cochrane review, they increase the energy intake by about 400 (175 to 1350) kcal

daily when completely finished [186]. However, supplements can reduce the spontaneous intake of normal food thus masking a lower food intake in the elderly [108, 187]. A large body of evidence shows the remarkable influence on outcome [188, 186]. Muscle functions and the quality of life have been improved in patients with non-neoplastic gastrointestinal diseases. Moreover, the rehospitalisation frequency was lower in comparison to patients treated with dietary advice only [173]. An additional mean intake of 407 kcal via ONS for two months resulted in the conservation of the body weight in elderly patients [189]. Even mortality was reduced in undernourished patients if the ONS were taken sufficiently [188]. Meanwhile, ONS are well manageable but the compliance is low outside study settings [190, 191, 192, 193]. Reasons comprise draw-backs in palatability and sensory aspects leading to taste fatigue [49, 194]. However, taking supplements like medication (i.e. several times a day a small volume) may be an option to raise acceptance and energy intake [195, 196]. An increase in energy intake may thus depend on supplement acceptance [197], which in turn shows that ONS may not be suitable for all patients.

Individualisation, decentralisation and staff education

A patient-driven individual multifactor approach may be the best option to increase food intake. A dietician/dietetic assistant and a nurse provided nutritional support and achieved increased energy and protein intakes in two studies [198, 199]. However, training the standard ward staff in nutrition did not increase the food intake [200]. Furthermore, nutritional support provided by assistants additional to the ward staff and trained in nutrition did not increase food intake in mal- and well-nourished geriatric patients [201]. In contrast, a questionnaire-based Scandinavian study found that if the ward staff is aware of malnutrition and several nutrition strategies were implemented, then nutrition care was improved [202].

The patients' satisfaction with the catering service has been shown to be important for food intake [69]. A room service-like catering increased patient satisfaction with the food service and led to higher intakes of energy and protein in children having cancer [203]. However, dining with a family member did not [204]. A decentralised bulky food production system increased food intake and in contrast decreased wastage in comparison to a plated system [205]. A Danish study found an improved food intake and reduced amounts of wastage with a buffet-like catering system for dinner. Patients thereby chose their food individually and more flexibly on the ward. Increased intakes (from 128 KJ to 560 KJ per patient) were reported for those patients with insufficient intakes. Patients eating adequately with the old system did not increase their intakes [68]. In contrast, in-between meals offered by a manned trolley did not increase the energy nor the protein intake in a second Danish study [206].

Restrictive diets and starvation

The plausibility of specific diets is currently more and more questioned because diets may increase the malnutrition risk especially in elderly patients [207, 208]. For surgery patients it has been shown that the postoperative feeding can progress quickly and

specific modified diets do not show advantages [209, 210, 211]. In contrast, surgery may even be delayed in order to improve the nutritional status in severely malnourished patients [212]. The need for a texture-modified diet may closely be re-evaluated since food intake can be less than with a normal diet [213]. The diabetic diet and diabetic food products are meanwhile considered obsolete in Germany [214]. Moreover, the effect of a weight-reducing diet in hospitals can be questioned as the nutrient intake is more likely decreased to an insufficient intake [215, 216]. Attention should be paid to frequent and prolonged nil-by-mouth times [78]. In particular, a carbohydrate drink can safely be applied until two hours before an operation or investigation with risk of aspiration due to anaesthesia. The stomach has been shown to be empty in sufficient time and insulin resistance was shortened after surgery thus reducing the stress response and even the length of hospital stay [217, 218].

Medication to promote appetite

Appetite stimulants may be applied to counteract anorexia. In animal models investigating muscle degradation promising results have been obtained, for example, in tumor bearing rats [219]. Especially progestins, corticosteroids or recently cannabinoids were thought to promote the appetite but their use is controversial. So far, there is only little evidence to draw a conclusion from animal models to human beings. Although the sensation of appetite was found to be better under a cannabinoid in AIDS patients, there was no significant effect on the body weight or other outcome parameters [220]. A review of megestrol acetate showed neither influence on the quality of life nor the survival rate in cancer patients [221]. Because of unsatisfactory results and side effects these drugs are thus limited to research and palliative care [222, 223].

1.5.2 Improving food intake by factors related to hospitalisation

Optimal treatment of disease and side effects

Drawbacks in the treatment of disease or even treatment failures may also influence food intake directly or indirectly. It was shown in a prospective study that patients' food intake is significantly decreased during treatment episodes, whereas between treatments the intake returned back to normal [73]. Also, a low food intake correlated with symptoms related to treatment side effects in patients with acute leukaemia receiving polychemotherapy [224]. Cancer patients suffering pain were more often malnourished than those without pain [60]. Minimal invasive procedures and sufficient pain relief reduce the stress response due to surgery and therefore are beneficial for the nutritional status and even morbidity and mortality [225, 226]. Furthermore, an adequate pain treatment may increase the energy and protein intake shortly after surgery [227]. The reduction of both postoperative ileus and opiod side effects provide a beneficial environment for early oral nutrition [226, 228]. First of all, adequate disease treatment is important to avoid the aggravation of disease thus requiring artificial nutrition or rehospitalisation [229].

Human resources and protected mealtimes

The hospital environment has profound influence on the food intake not only because of being unfamiliar to the patients but a daily routine which is unfavourable for eating [57]. Patients often experience extended nil-by-mouth times, although it was shown that two hours of starvation are sufficient before anaesthesia [78]. A couple of studies investigated whether protected mealtimes, i.e. periods during the day reserved for food intake or providing help with eating, influence food intake [163, 230, 231]. Indeed, in the United Kingdom (UK) a campaign was launched to introduce protected mealtimes in hospitals all over the country [232]. Currently, the results are still inconsistent mainly due to challenges related to the implementation of protected mealtimes [233, 234]. However, a successful implementation of protected mealtimes together with further interventions like an improved catering and the screening for malnutrition resulted in decreased prevalence rates of malnutrition [235].

A recent German-wide study among 10,000 nursing staff revealed that basic care procedures cannot be provided due to staff reduction and work overload while patient numbers increase. However, providing nutritional assistance during mealtime requires additional time [236]. About one in three nurses state that patients are not assisted adequately during mealtime. Among the most exhausted nurses every second states that nutritional assistance is often not provided adequately [17]. Furthermore, the interaction between patient and nurse during the mealtime has been shown to be beneficial for the energy and protein intake [237]. In addition, patient-nurse ratios are related to general morbidity such as catheter infections during parenteral nutrition [238].

1.6 Shortcomings of nutrition studies

As shown above, numerous descriptive studies elucidate the implications of malnutrition on several outcome measurements [168]. However, they do not present the causal link between malnutrition, their causes and their consequences. In fact, malnutrition affects severely ill or terminal patients more often than healthy people or those with mild diseases. Vice versa, a severe disease can lead to malnutrition. Especially, outcome parameters like mortality and length of hospitality are obviously influenced by several factors apart from malnutrition (e.g. hygiene, severity of disease, age [239]). Whether the relation of malnutrition and a worse outcome reported in descriptive studies is causal and hence reversible can thus only be determined by well-designed intervention studies. Unfortunately, results of hard outcome intervention trials have been rather heterogenic up till now. The transferability outside a study setting is questioned especially concerning oral supplements. For ethical reasons there is no study of nutritional support vs. no support in risk patients. Often, control patients receive dietary advice being either superior or inferior to the test intervention, i.e. ONS intake. Thus, patients in Portugal [114] seem to be better advised than patients in Berlin [173]. Therefore, studies are hardly comparable. For practical reasons historic control groups are compared to present intervention groups in case a nutritional protocol was newly introduced to

a whole ward [240, 215]. A considerable number of biases may then influence the results. Finally, large study populations are crucial to achieve sufficient statistical power for hard outcome studies. In multi-centre studies, however, interventions and settings are less homogenous, thus complicating the disclosure of nutritional effects.

So far, nutritional support including normal food has not been considered extensively. In contrast, the European Council resolution ResAP 2003(3) on food supply in hospitals stated that first of all normal food shall be chosen for the prevention and the treatment of malnutrition [241]. If patients do not meet their requirements, fortifications and finally ONS can be used. The latter shall be an addition and no replacement. Until the preparation of this script, only three studies had investigated the effect of a multifactor intervention that conforms with the classic concept of "nutritional therapy" in hospitalised patients. They present opposing results most likely due to statistical deficits, i.e. heterogeneous study populations, bias and insufficient nutritional interventions. Thus, there is need for more randomised controlled intervention phase III trials [19].

2 Preliminary work and study preparation

2.1 Results of the pilot study

Two minor investigations were performed at Kantonsspital Liestal hospital previously to the intervention study. First, anthropometric parameters describing the nutritional status (body weight, body height, BMI, body weight change) were investigated in 107 patients' charts in October 2005. At admission, in 60 % of the charts body weight and height was recorded but in 13 % only, the BMI was calculated. Body weight change, i.e. a second measurement of body weight during hospitalisation, was registered in one fourth of patients. These results indicate that patients with a risk of malnutrition are not routinely detected.

From December 2005 to January 2006 an investigation on food supply was performed [169]. The amount of food that was eaten by the patient was visually estimated in 1178 menus. Quantities of 0 %, 25 %, 50 %, 75 % or 100 % in comparison to the initial amount were defined with the help of the 4-quadrant model. Less than half of all portions (46 (5) %) were finished completely. A waste rate of 24 (1) % was calculated. Up to one third of all meals were ordered as "semi portion" and not finished more often than a full portion. Although the offered menus showed sufficient nutrient content, the energy intake was remarkably reduced. Less than 1500 kcal/d were consumed by the majority of patients (the mean energy intake was 1340 (357) kcal/d). The nutrient intake was concluded to be insufficient and considered a risk factor in the management of malnutrition.

2.2 Preparations for the randomised controlled intervention trial

2.2.1 Record sheets applied in the trail

Data record sheets were developed in order to collect all study data efficiently. For patient recruitment a continuously numbered recruiting list was compiled. For admission and discharge data the standard NRS-2002 sheet was modified. Main outcome parameters were added, i.e. patient code, body weight, height, diagnoses, medication, and date of admission. Check boxes for further analyses (blood) and the follow-up data were added in order to improve integrity. A detailed anamneses sheet was applied with each intervention patient. Interventions were recorded on an individual record sheet for each patient. All sheets were tested before the start of the study in order to identify practicability and are compiled in the appendices A.2.

2.2.2 The intervention strategy of the trial

A concept for the nutritional support was developed that was based on the pilot studies [169] and the literature research (see Introduction). Although there is little evidence, there is consensus that nutritional support should conform to a stage model preferring the more natural and simple way of food intake to the more artificial/invasive way [242]. Studies show fewer complications, an easier handling and lower costs for natural food compared with artificial nutrition [243, 244, 245]. However, details of such a strategy have to be defined individually according to the patient's need. Since natural food is the preferred nutrient source in this study, the two first stages of nutritional support are the most important, i.e. abolish eating barriers and individualise food ordering and intake. Additionally, oral nutritional supplements, food fortification and in-between snacks are provided. Aspects related to individualisation, dietary counselling, decentralisation, timing of support, restrictions and side effect treatment are also realised (for details refer to 1.5.1 and 4.2. Basically, interventions conform to the ESPEN guidelines for enteral nutrition (see www.espen.org and [177]).

Energy requirements as an intervention target

The patients' daily individual needs on energy and protein determine the extent of nutritional support. In order to define the intervention target, the total daily energy expenditure (TEE) can be estimated. Thereby the resting energy expenditure (REE), accounting for about 60 %, provides the basis of TEE [246]. The latest investigations on REE were published by Mueller et al. [247]. Retrospectively, data of indirect calorimetry measurements in seven research centres in Germany was analysed and cross-validated. REE-equations according to different BMI groups were developed, taking the high prevalence of adipose and obese (otherwise healthy) people into account. A comparison of equations revealed that the normal body weight equation may best fit to our study population (see equation 2.1) while others have shortcomings (e.g. low and high BMI equation by Müller et al., WHO, Harris-Benedikt [248, 249, 250, 251]).

$$REE(kcal) = (0.02219 \times bodyweight + 0.884 \times sex - 0.01191 \times age + 0.02118 \times height + 1.233) \times \frac{1000}{4.18} \quad (2.1)$$

The majority of patients - although being malnourished - were expected to belong to the "normal BMI" group (18.5-25 m/kg2). In order to calculate REE in obese people, an adapted body weight was used, which can be adjusted by the same stress factors used for underweight and normal weight people. To calculate the adapted body weight, half of the difference between ideal and actual body weight was added to the ideal body weight [252].

About 30 % of the TEE depend on the physical activity of a person. Thus a factor defining the physical activity level (PAL) has to be added (see table 2.1). As patients

Table 2.1: Physical activity level and stress factors

Condition/disease	PAL or SF	Condition/disease	PAL or SF
Sleeping	1.0 [254]	Limited mobile	1.2 [252, 254]
Bed-bound	1.1 [255]	Mobile	1.3 [252]
BMI<18	1.2 [252]	Small surgery	1.2 [252]
Sepsis	1.3-1.4 [252]	Short-term fasting	0.9-1.0 [252]
Intestinal Bowel Disease	1.0-1.1 [252]	Decubitus	1.0-1.3 [256, 83]
Haematological disease	1.3 [252]	Long bone fracture	1.3
Myocardial infarct	1.1	Pancreatitis	1.1-1.2 [252]
Cancer	1.1-1.3 [252, 89]	Liver disease	1.0-1.2 [252, 257]
High temperature	1.1/°C [252, 258]	Convalescence after surgery	1.1-1.3 [259]
Severe infection	1.3 [252]		

mainly are bedbound and the energy expenditure through exercise (i.e. PAL) is kept to a minimum, the total energy expenditure is mostly less than under healthy conditions. However, during disease metabolic stress may increase the REE. Hence, a stress factor (SF) is needed to adjust the REE [253] (see equation 2.2). However, these SF are not available for the majority of diseases and vary even within one diagnosis group. Barak et al. published a large number of stress factors for different diagnoses [252]. These stress factors were compared to other publications and finally provided the basis for our study intervention (see table 2.1). The majority of stress factors range between 1.1 and 1.3 and thus form a frame with only little inter-disease variability and tolerable error margin. However, short-term evaluations of the intervention are still necessary in order to ratify the right treatment strategy. As the aim of the study was to compensate a deficient nutrient intake "as well as possible" in patients with a highly variable metabolism, exact individual requirements were not crucial.

$$TEE(kcal) = REE \times PAL \times SF \tag{2.2}$$

Protein requirements as an intervention target

As with energy, expert opinions about the daily protein requirement differ widely [260, 261]. Numerous conditions are known where a low protein intake has positive effects [262, 263]; however, recommendations on protein intake have been adjusted upwards year after year [264, 265]. Evidence on protein requirements is most of all based on nitrogen balance studies showing a not negligible number of shortcomings and small population groups [266, 261]. On the other hand, the variations in metabolic stress (see above) within a disease group also influence the energy balance and thus nitrogen

balance and protein requirements [267]. Current guidelines recommend elevated protein requirements during mild to moderate disease [268, 269, 270]. The minimum amount of 1g protein per kilogram body weight was assumed to be necessary to achieve nitrogen balance in geriatric patients, during mild pancreatitis, in cancer patients and acute renal failure [271, 59, 272, 265]. Furthermore, proteins contribute to about 15 energy per cent of total energy intake in a natural mixed diet. Thus, about 1g protein per kg body weight is consumed with a diet containing 15 energy percent provided by protein (variations depend on the body weight). Since the intervention was planned to mainly consist of natural food, a protein intake of 1 g/kg body weight was thus constituted the intervention target. More elevated protein targets would be hard to achieve with mainly normal food.

3 Hypothesis and study objectives

3.1 Hypothesis

The intake of food is reduced during hospitalisation according to the literature and our pre-investigations. Besides, a malnourished condition is related to a worse outcome. Especially patients with a malnutrition risk may profit from nutritional support but unfortunately are not detected at hospital admission. We assume that by increasing food intake in patients who are malnourished or at risk of malnutrition the outcome can be improved. However, the statistical approach must be well thought-out. Otherwise, the impact of nutrition might be concealed. Therefore, only patients with a high chance of profiting from nutritional support must be included (i.e. risk patients screened by NRS-2002, no terminal patients). The study setting, notably the interventions and their evaluation, must be homogenous. Interventions should be monitored and if not successful (e.g. food was not consumed), compensation must be organised directly. A successful intervention, i.e. an increased food intake, limits our hypothesis. If no improvement in food intake is achievable, patients with a risk of malnutrition are simply sicker than those without, i.e. the outcome criteria are exclusively influenced by the disease and not essentially by nutrition.

3.2 Study objectives

The aim of the present study was to develop and evaluate a routinely manageable concept for an improved nutritional care of malnourished in-hospital patients defined by NRS-2002.

4 Patients and methods

4.1 Randomisation and study inclusion

The study was conducted as a randomised controlled intervention trial from January 2007 to November 2007 (intervention period; follow up until June 2008) until a sufficient number of patients had been recruited (see statistics). The study protocol was approved by the ethic committee of the University of Basel/Switzerland. All patients were informed about study objectives and procedures and signed written informed consent before the inclusion.

During the study period, all adult patients consecutively admitted to the general medical ward at "Kantonsspital Liestal" hospital were screened for their nutritional risk using the NRS-2002 questionnaire. Exclusion criteria were: no informed consent, terminal condition, expected stay less than 5 days (judged by physician), previous participation in this study, being on starvation or parenteral nutrition, and/or being on dialysis. Patients with a nutritional risk (i.e. a NRS-2002$\geq$3) were recruited and randomised to the intervention group (IG) or the control group (CG) according to a computer-generated randomisation list. Thus, patients received either individualised nutritional support for 5 to maximum 28 days (IG) or standard hospital care (CG). Patients with an initial score below 3 were re-evaluated weekly during the study's intervention period and asked for participation in case a nutritional risk developed during hospitalisation.

4.1.1 Study endpoints and data collection

The primary endpoints of the study were the average daily energy and protein intake. As secondary parameters the changes in body weight during hospitalisation, number of complications, number of antibiotic therapies due to infectious complications, length of hospital stay, quality of life Short Form 36 questions (SF-36) questionnarie, hospital re-admission (six months after discharge), mortality (hospital and six months after discharge), compliance with oral nutrition standard supplement consumption and plasma concentrations of 25-OH-D_3, ascorbic acid and glutathione were evaluated.

All baseline measurements were made within 72 hours after admission. Body weight was measured in all patients on a chair scale (100 g precision) in light clothes without shoes in the morning. The body weight of patients with oedema was recorded at admission, as was the body weight of patients being dehydrated. No corrections for dysbalances of the water balance were applied. Body height was asked or taken from the personal identity card. The sensitivity of self-reported height was judged sufficient for our study purpose [273]. In case body height was not available it was measured using a stadiometer (1 cm precision) or transposed from knee length measurements (when the patient was

not able to stand upright [273]). Quality of life was recorded by the SF-36 questionnaire filled out either by the patients themselves or by an experienced interviewer. Venous blood samples were taken after an overnight fast by the nurses on duty. Throughout the study period, the intake of medication and new complications were recorded daily and confirmed by the physician on duty. Complications were defined as all hospital acquired unexpected events, i.e. all diagnoses apart from the diagnosis leading to hospitalisation occurring at least 5 days after admission. These include infectious complications (respiratory tract, urinary tract, wound, catheter infection and others) and non-infectious ones (decubitus, wound dehiscence, abscess, respiratory failure, cardiac arrest, insufficiency or arrhythmia, diarrhoea (non-infectious), pneumonia, gastroenteritis, liver and kidney failure, cerebral bleeding, thrombosis and others). Complications were diagnosed and recorded by the physicians (who were not involved in the study) according to local hospital guidelines.

Before discharge (i.e. the decision of the responsible physician) all baseline measurements were performed again. The actual length of stay (LOS) based on admission and discharge dates and the possible LOS (based on admission dates and the physicians estimate of when the patient was ready to be discharged) in the general medical ward and in hospital were calculated.

4.2 Nutritional intervention

Patients of CG received standard nutritional care including the prescription of oral nutritional supplements and nutritional therapy prescribed by the physician independently of this study and according to the routine ward management.

Patients of IG received individual nutritional care, including a detailed nutritional assessment, individual food ordering, fortification of meals with maltodextrin, rapeseed oil, cream and/or protein powder, in-between snacks and oral nutritional supplements. Nutritional interventions were applied according to the patients' need and preferences. Main meals were ordered according to the menu. Simple variations in order to meet the patient's taste were ordered directly in the kitchen. Texture modifications were offered if needed, but avoided whenever possible due to disadvantages (refere to 1.5.1). In-between meals, mostly easy to swallow and fresh items, i.e. dairy products blended with fresh fruits, were offered one to two times the day. In-between meals were stored in the ward's kitchen fridge until served. Depending on the patient's compliance, ONS was offered at room temperature, cooled or frozen as ice. Different tastes were tried in order to increase compliance. All interventions aimed at meeting the daily energetic requirement according to the individual total energy expenditure (TEE; calculated from resting energy expenditure (REE) corrected by an individual factor for physical activity level (PAL) and disease (stress factor, SF)). Protein intake was set at 1.0 g/kg body weight. Complications influencing feeding (e.g. nausea) were reported to the ward physician and treatment was optimised (e.g. medication).

4.2.1 The evaluation of food intake

Reference menus were weighted to have the detailed size/weight of each food item and the corresponding energetic and protein contents were calculated (with PRODI® basing on the German Bundeslebensmittelschlüssel II.3,). Food intake was observed during meal times. The consumed part of each food item was visually estimated and recorded. In case less than 75 % of the portion (i.e. served food at one meal with known energy/protein content) offered had been consumed, energy and protein intake was compensated on a daily basis by supplying either ONS (Resource (Nestlé Nutrition)) or in-between meals in IG. Snacks, drinks and ONS which were additionally consumed were reported by the ward staff and the author or the patients have been asked for. In case of starvation before invasive investigations or surgical procedures a lipid-free ONS was used instead of the standard ONS. Finally, with the help of PRODI® database, each daily kcal and protein intake was calculated based on the consumed food items. Food which was not in the database (e.g. fortified drinks or personal snacks) was entered before calculation. Energy given by the intravenous route, e.g. 5 % glucose solution, was added to the oral intake. Except of energy and protein intake, all outcome data were blinded in terms of that physicians and nurses who were responsible for the outcome did not have access to group allocation.

4.2.2 The evaluation of ONS compliance

The compliance of ONS consumption was analysed for standard ONS only and presented in two ways. First, compliance of ONS intake in % was calculated by taking the amount of ONS consumed divided by the amount the patient should have consumed and multiplied by 100. According to manufacturer information the consumption of ONS can be improved by f. ex. cooling, blending with other food, portioning etc. The volume consumed was therefore corrected and transformed into a five-point compliance score (adapted from Spillmann et al. [274]). On the one hand, corrections involved the additional afford (help) that was needed to prepare the ONS since time at the ward was limited. On the other hand, the patients' reliability was considered. Taking the ONS too late (i.e. too close before the next main meal (like a "pre-meal snack")) may decrease the amount of food consumed at main meals [275, 187]. Taking the complete ONS without any help and high reliability then means five points. Taking it completely but too late (no reliability) means four points, as means taking all with much help (i.e. more than bringing the drink, opening it and putting the straw into it). A person who consumed 25 % only and needed a lot help or had no reliability then receives one point.

4.3 Blood sampling and analyses

At admission and before discharge, venous blood was withdrawn into heparinised tubes and directly centrifuged. The plasma aliquots for 25-OH-D_3 and glutathione were frozen and stored at -80 °C until the analysis. Plasma specimen for ascorbic acid analysis were deproteinised and stabilised using meta-phosphoric acid-perchloric acid solution and

stored at -80 °C until analysis. Frozen samples were transported to the central lab in Bonn. Ascorbic acid detection was carried out by HPLC with UV detection [276]. The analysis of 25-OH-D_3 was achieved by enzymatic immunoassay (ELISA kit from IDS Frankfurt/Germany) and the detection of glutathione after separation of metabolites by fluorescence detection [277].

4.4 Follow-up

Information concerning the re-admission and 6-months-mortality was obtained by the patients hospital computer register or by calling either the patients themselves or their general practitioners, respectively, six months after discharge.

4.5 Statistical analysis

The level of statistical significance was set at $p<0.05$. A p-value between 0.05 and 0.1 was considered a statistical trend. Sample size (with a power of 0.9, two-sided, $p=0.05$) was calculated based on an increase in energy intake by 15 % (285 kcal; effect size). The standard deviation of energy intake calculation has been taken from the pilot study (see preliminary investigations and [169]). Including a 15 % drop out rate, at least 60 patients were required per study arm. Statistical analyses were performed using SPSS 13.0. Normal distribution was verified using statistical tests (Shapiro-Wilk and Kolmogorov-Smirnov test) and graphical methods (box plot, histogram and normal Q-Q plot). The effect of intervention was tested by repeated measure ANOVA. Statistical differences of the baseline and outcome data were tested by Chi^2 or Fisher's exact test (binary data) and by Mann-Whitney- or independent samples t-test (quantitative data). The baseline SF-36 QoL study data was compared to a normal reference population using one way ANOVA (Welch statistic). Variance homogeneity was checked using Levene's test and post-hoc analysis performed with the Games-Howell test. All results are presented as mean (standard deviation) unless otherwise indicated.

5 Results

5.1 NRS-2002 screening and patient recruitment

In total, 767 patients were consecutively admitted during the study period including 271 who were registered with an NRS-2002≥3. According to the predefined criteria, 137 patients were excluded among those patients at parenteral nutrition (for details refer to figure 5.1). Patients with psychiatric disorders or severe dementia were listed under "no I.C.". Unconscious patients rank among the group "nil per mouth". Allowing for 57 patients who were readmitted and excluding terminal patients, the patient-related malnutrition risk prevalence was 32 % for all admitted medical patients. The subgroup prevalences are presented in table 5.1.

Table 5.1: Malnutrition risk prevalence rates

Patient group	Frequency	NRS-2002[1]≥3 (%)
All	232 of 684	34
All medical	231 of 672	35
All medical excl. terminal	206 of 647	32
Non-medical	1 of 12	8
Dialysis	3 of 10	30
Non per os	7 of 7	100
Short hospitalisation	16 of 50	32
No I.C.[2]	56 of 56	100
Terminal	25 of 25	100

[1] Nutritional Risk Screening 2002
[2] Informed Consent

Finally, 134 patients were equally randomised to CG and IG, respectively. Due to a wrong initial diagnosis, one patient in each group had to be excluded because a malnutrition risk according to NRS-2002 was no longer detectable. Thus, the Intention-To-Treat population (ITT) consisted of 132 patients with each 66 patients in IG and CG, respectively. All but 16 patients were included at admission. Those 16 developed a nutritional risk during hospitalisation and were included after 7 (7) days. Due to protocol violations (death or discharge before the minimum intervention period (n=13) and withdrawal of informed consent (n=1)) further 14 patients were excluded from the Per-Protocol population (PP).

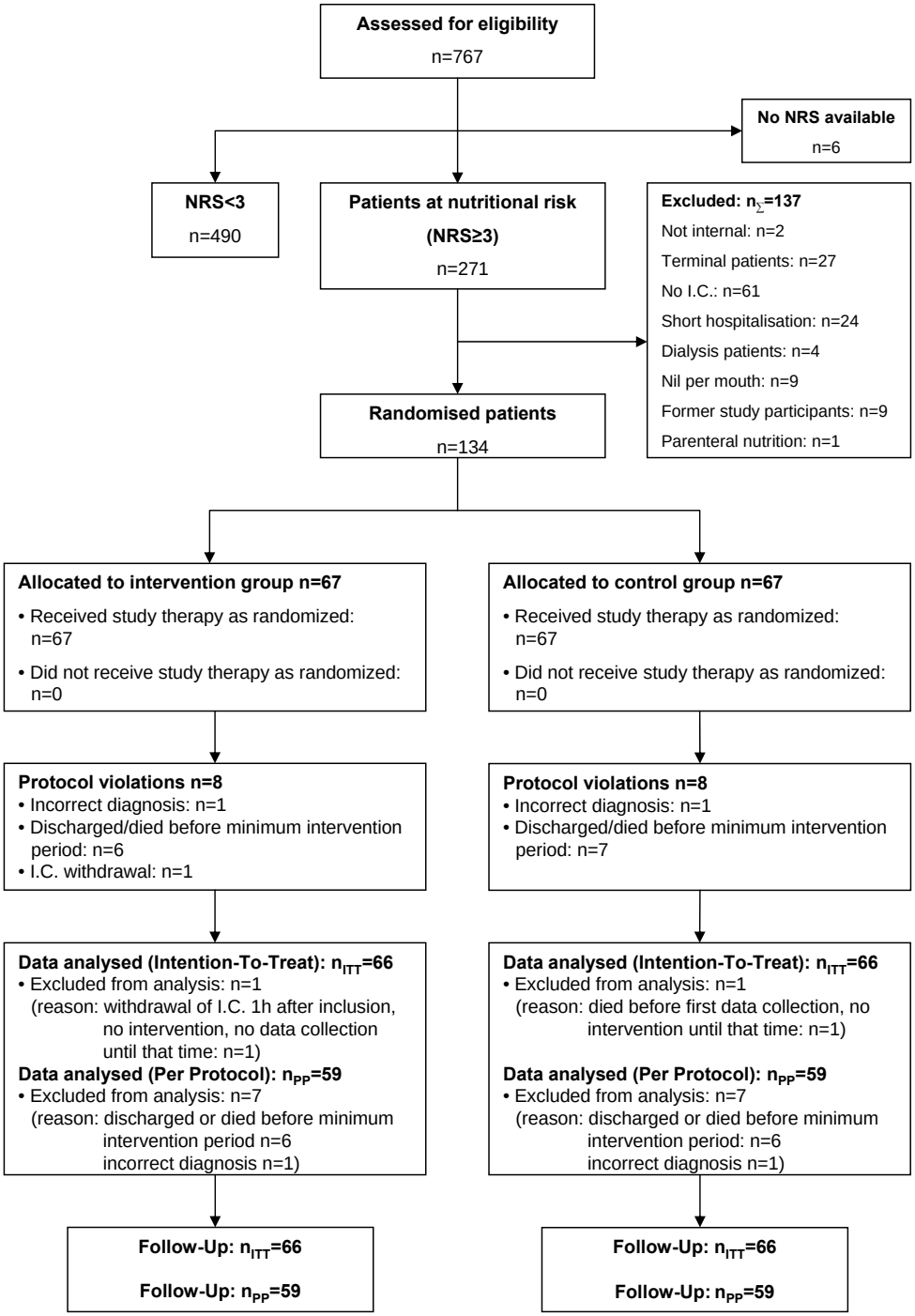


Figure 5.1: Study flow chart

5.2 Baseline characteristics of the study patients

The baseline demographic and clinical data of patients in IG and CG (n=66 each) are given in table 5.2. The majority of patients were women (CG: 40/66 vs. IG: 47/66; p=0.271). Height, body weight, BMI, initial diagnoses, average NRS-2002 subscores, number of oral drugs, REE, TEE, SF/PAL and QoL did not differ between groups.

Table 5.2: Baseline data

Variable	Randomisation	Mean (SD)	Median (min-max)	Variance	Significance
Age	CG[1]	75 (11)	76 (43-94)	113	0.091
	IG[2]	70 (16)	73 (21-94)	267	
Height	CG	165 (10)	165 (147-192)	100	0.633
	IG	166 (8)	165 (148-190)	65	
Body weight	CG	66.1 (16.2)	65.6 (29.6-99.0)	262.9	0.504
	IG	68.1 (16.9)	67.4 (39.7-119.0)	286.1	
BMI	CG	24.1 (4.9)	23.6 (13.2-42.3)	24.0	0.527
	IG	24.6 (5.3)	24.3 (14.9-38.4)	27.9	
NRS-2002 disease score	CG	1.0 (0.3)	1 (0-2)	0.1	0.057
	IG	0.9 (0.5)	1 (0-2)	0.2	
NRS-2002 nutrition score	CG	1.7 (0.7)	2 (0-3)	0.5	0.233
	IG	1.8 (0.6)	2 (1-3)	0.4	
Number oral drugs	CG	7 (3)	7 (0-12)	7	0.465
	IG	6 (3)	6 (1-14)	9	
REE	CG	1352 (207)	1328 (970-1785)	42802	0.845
	IG	1359 (188)	1327 (1068-1768)	35442	
Sum of SF and PAL	CG	1.3 (0.1)	1.3 (1.2-1.4)	0.0	0.107
	IG	1.3 (0.1)	1.3 (1.1-1.4)	0.0	
TEE	CG	1733 (258)	1721 (1272-2321)	66810	0.907
	IG	1728 (227)	1712 (1348-2211)	51316	

[1] Control Group
[2] Intervention Group

A mild stress metabolism (subscore 1) and a moderate nutritional impairment (subscore 2) were most often allocated during the NRS-2002 screening. In 62 patients the nutritional subscore was given because of a reduced food intake. Weight loss led in 26 patients and both of these criteria in 43 patients to the respective subscore. The nutritional subscore covered the whole range of possible disorders (i.e. subscore 0 to 3) whereas the disease severity subscore 3 (typically describing ICU patients) was not assigned. Baseline mean estimated REEs were equal among groups (table 5.2). The factor to ajust REE (i.e. the sum of PAL and the disease derived Stress Factor) was 1.3 (0.1) in both groups. Thus the calculated TEEs were similar between groups (table 5.2) although a wide range of the TEEs from 1272 to 2321 kcal was observed.

All initial diagnoses according to ICD-10 coding are given in table 5.3. One third (41/132) of all patients was hospitalised due to main or secondary diagnosis related to a malign tumour. The majority of patients was hospitalised because of a disease related to the cardio vascular system (100/132). In addition, 49 out of 132 patients received diuretics (no group difference) in order to promote weight loss because of cardiac insufficiency. Polypharmacy was common. In IG 39 of 66 patients and in CG 44 of 66 patients (p=0.471) received more than five oral drugs. Nine patients received nutritional therapy prescribed by the physician (CG: 4/62 vs. 5/61, p=1.000).

Table 5.3: Diagnoses according to ICD-10 coding[3]

ICD-10 code	Randomisation	Frequency
Infectious and parasitic	CG[1]	10
disease	IG[2]	4
Neoplasms, diseases	CG	17
of the blood	IG	13
Endocrine and metabolic diseases,	CG	11
diseases of the digestive system	IG	12
Diseases of the nervous system,	CG	2
the eye and adnexa	IG	5
Diseases of the	CG	14
circulatory system	IG	15
Others	CG	12
	IG	17

[1] Control Group
[2] Intervention Group
[3] International Classification of Diseases (10^{th} edition)

The baseline quality of life scoring is given in table 5.4. No differences appeared between groups. However, all values were reduced compared to a healthy reference population (refere to the appendices, section A.4).

Table 5.4: SF-36 baseline data[b]

Scale[a]	Randomisation	Mean (SD)[c]	Median[c] (min-max)	Variance	Significance
SF-36 PF	CG[1]	25 (25)	20 (0-85)	606	0.357
	IG[2]	25 (24)	20 (0-95)	582	
SF-36 RP	CG	4 (9)	0 (0-25)	78	0.525
	IG	10 (24)	0 (0-100)	590	
SF-36 BP	CG	49 (33)	41 (0-100)	1112	0.117
	IG	42 (35)	32 (0-100)	1199	
SF-36 GH	CG	50 (20)	50 (15-95)	414	0.493
	IG	51 (19)	52 (10-100)	376	
SF-36 VT	CG	27 (19)	25 (0-75)	349	0.216
	IG	22 (19)	15 (0-90)	368	
SF-36 SF	CG	69 (31)	75 (0-100)	977	0.117
	IG	58 (33)	63 (0-100)	1068	
SF-36 RE	CG	54 (48)	67 (0-100)	2260	0.642
	IG	50 (49)	33 (0-100)	2423	
SF-36 MH	CG	64 (17)	60 (36-100)	276	0.073
	IG	59 (20)	56 (16-100)	410	
SF-36 PCS	CG	27 (7)	26 (10-42)	48	0.437
	IG	28 (8)	28 (10-47)	64	
SF-36 MCS	CG	48 (11)	48 (25-69)	130	0.081
	IG	44 (12)	44 (24-66)	143	

[a] SF-36 abbreviations: PF-Physical Function, GH-General Health, RP-Role Physical, BP-Bodily Pain, SF-Social function, RE-Role emotional, MH-Mental Health, VT-Vitality, PCS-Physical Component Summary, MCS-Mental Component Summary

[b] for all SF-36 sub- and summary scales: n=49 (CG) and n=55 (IG)

[c] in %

Baseline plasma levels of ascorbic acid (IG: 34.2 (21.1) vs. CG: 27.2 (20.4) μmol/l) and glutathione (IG: 4.07 (2.36) vs. CG: 3.76 (1.98) μmol/l) were comparable in both groups. In contrast, 25-OH-D_3 concentrations were higher in IG (51.9 (23.7) nmol/l vs. CG: 44.8 (25.5) nmol/l; p=0.020, table 5.5). However, the number of patients with concentrations below the reference for healthy people was equal in both groups (table 5.6). One third of all patients (43/132) showed ascorbic acid values below the reference level of 17 μmol/l. For 25-OH-D_3 (25 nmol/l), only 12% (16/132) and for glutathione (2.2 μmol/l) one quarter (33/132) showed low levels (no differences between groups). No seasonal differences in 25-OH-D_3 levels were found.

Table 5.5: Micronutrient baseline concentration

Micronutrient	Randomisation	Mean (SD)	Median (min-max)	Variance	Significance
Ascorbic acid	CG[1]	27.2 (20.4)	23.1 (1.0-92.7)	416.3	0.056
	IG[2]	34.2 (21.1)	32.0 (1.6-96.0)	444.9	
25-OH-D_3[3]	CG	44.8 (25.5)	35.8 (13.2-128.9)	652.7	0.020
	IG	51.9 (23.7)	47.8 (14.6-134.9)	562.9	
Glutathione	CG	3.76 (1.98)	3.60 (0.36-9.00)	3.94	0.503
	IG	4.07 (2.36)	3.96 (0.32-14.99)	5.57	

[1] Control Group
[2] Intervention Group
[3] 25-Hydroxycholecalciferol

Table 5.6: Number of patients with micronutrient concentrations below references for healthy people

Micronutrient	<Reference IG[2]	<Reference CG[1]	Significance
Ascorbic acid[5]	17/66	26/66	0.137
25-OH-D_3[3]	7/66	9/66	0.791
25-OH-D_3[4]	56/66	58/66	0.800
Glutathione[6]	16/66	17/66	1.000

[1] Control Group
[2] Intervention Group
[3] 25-Hydroxycholecalciferol, reference level:25 nmol/l
[4] Reference level: 80 nmol/l
[5] Reference level: 17 μmol/l
[6] Reference level: 2.2 μmol/l

5.3 Micronutrient therapies during hospitalisation

Different preparations of micronutrients were prescribed by the physicians independently of the study. However, compliance was not evaluated. Four patients (CG: 1, IG: 3; p=0.619) received ascorbic acid supplementation (a multivitamin pill with 180 mg ascorbic acid per day). Vitamin D was prescribed to 23 patients (CG: 10, IG: 13; p=0.647) as a combination preparation (500 mg calcium and 400 I.U. 25-OH-D_3 per day). Other vitamins were prescribed to 10 patients in each group (p=1.000) and minerals to 58 patients (CG: 31, IG: 27; p=0.599).

5.4 Nutritional interventions during hospitalisation

On every study day patients in IG consumed more energy and protein than patients in CG (refere to figure 5.2, next page). The repeated measure AONVA revealed a highly significant intervention effect for both protein and energy intake (p<0.001) after 5 and 10 days of intervention (see table 5.7).

Table 5.7: Intervention results

Variable	Randomisation	Mean (SD)	Median (min-max)	Variance	Significance rmANOVA[a]
Kcal/d	CG[1]	1115 (381)	1110 (485-2269)	145162	<0.001[b]
	IG[2]	1553 (341)	1518 (789-2827)	116586	
Protein/d	CG	43.9 (17.2)	44.8 (16.3-103.8)	296	<0.001[b]
	IG	65.4 (16.4)	65.7 (26.8-102.2)	270	

[1] Control Group
[2] Intervention Group
[a] Repeated measure ANalysis Of VAriance
[b] Intervention periods 5 and 10 days (with n=119 and n=70, respectively)

The nutritional interventions led to a significant higher absolute mean intake of energy and protein per day in IG compared with CG patients (table 5.7). The energy (IG: 24 (8) kcal/kg vs. CG: 18 (7) kcal/kg) and protein intakes (IG: 1.0 (0.3) g/kg vs. CG: 0.7 (0.3) g/kg) also differed significantly (p<0.001) when expressed as calories and gram protein per kg body weight. 55 patients (83%) in IG and 20 (30%) in CG reached a mean daily energy intake equal or above the 75% threshold of their individual estimated TEE. However, the mean estimated TEE was 175 kcal in IG and 618 kcal in CG higher than the actual mean daily caloric intake (both values p<0.001).

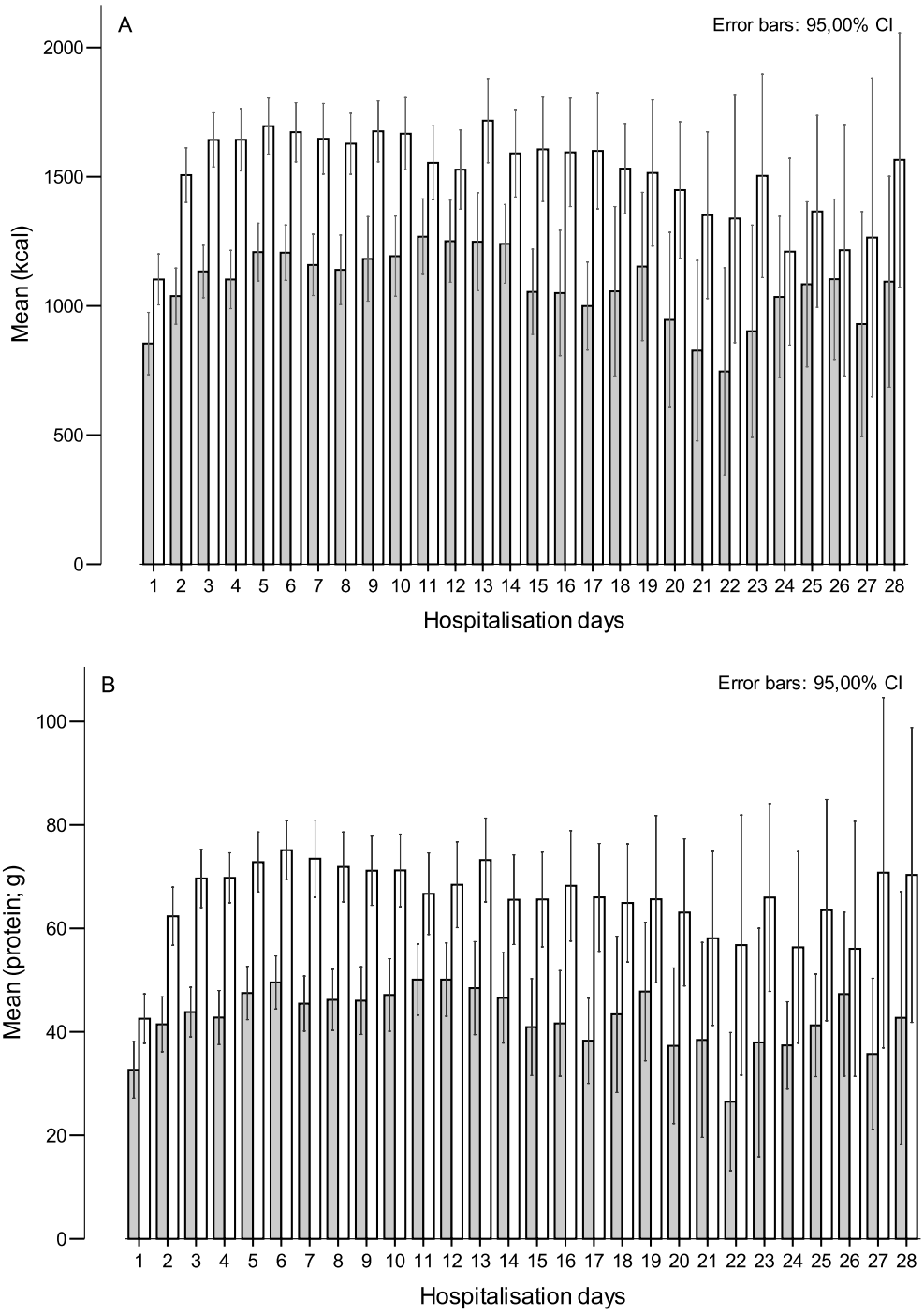


Figure 5.2: Caloric (A) and protein (B) intake according to randomisation (Control Group: shadowed bars, Intervention Group: white bars)

All patients in IG had at least one meal during their hospitalisation which was consumed less than 75% (see methods). ONS and/or in-between meals were therefore offered according to the patients' preference and compliance. In total, ONS covered 13 (11)% of protein and 9 (8)% of energy in IG and 3 (11)% of protein and 2 (8)% of energy in CG (for both values $p<0.001$ between groups). The main coverage of energy was achieved by normal food in both IG (86 (9)%) and CG (95 (11)%, $p<0.001$). The same applies to the total daily protein intake which was primarily covered by normal food (IG: 82 (12)% vs. CG: 96 (12)%, $p<0.001$). It contributed to energy supply by 18 (2) and 17 (3)% ($p=0.008$) in IG and CG, respectively. Regarding normal oral food only, the intake was highly significant between groups for both, energy and protein intake (see figure 5.3 and A.7).

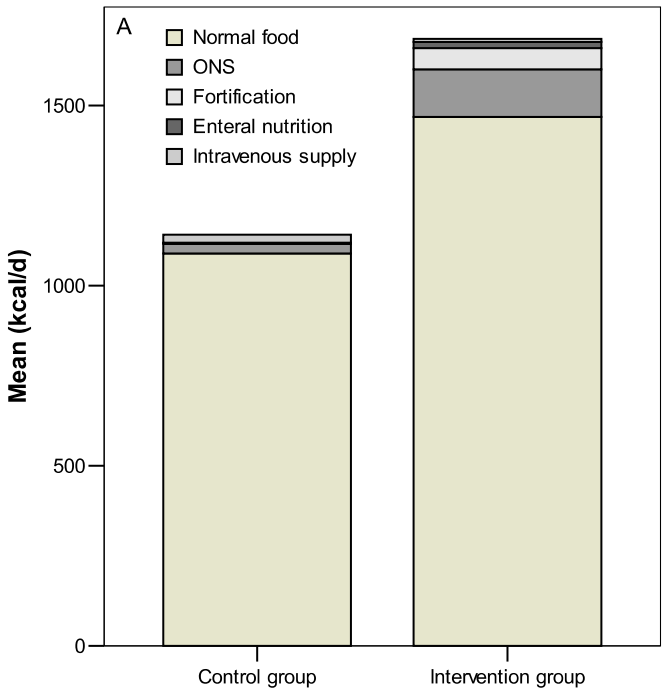


Figure 5.3: Caloric intake according to food type/intervention

In IG 27 (8) % of the total energy and 27 (10) % of the total protein was consumed as in-between snacks. For CG numbers were 11 (10) % and 9 (12) %, respectively, both differences highly significant between groups ($p<0.001$). The energy and protein intake were significantly different between groups at all meals except breakfast and a trend-like difference only at supper (see figure 5.3 and A.7).

Apart from ONS food fortification, enteral nutrition and intra-venous glucose/fat supply did not contribute considerably to nutrient intake (see table A.1 and A.2). In IG all but two patients received food fortification whereas only 12 control patients received fortified food by either the dietician or with milk shakes (standard fortified; $p<0.001$). Only three patients received enteral nutrition (CG: 1, IG: 2, $p=1.000$). Parenteral sup-

ply (which was not meant to nourish the patient, i.e. 5 % glucose, "Misch 2:1"- infusion and propofol injection) was responsible for a low percentage of total calorie supply in 45 patients (IG: 1 (2) %, CG: 2 (5) %; p=0.023).

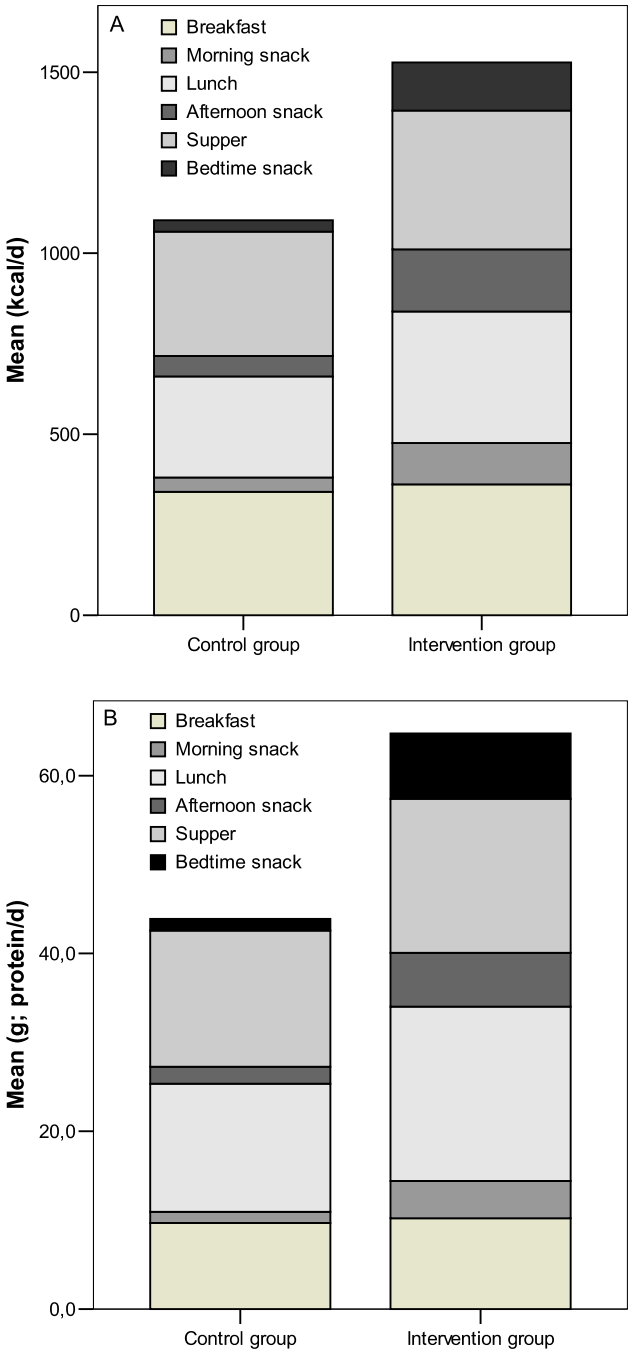


Figure 5.4: Caloric (A) and protein (B) intake according to meals

5.5 The compliance of ONS intake

In IG, 59 patients received standard ONS during hospitalisation. Six patients received lipid-free ONS due to a contraindication (e. g. fat malabsorption due to pancreatitis). One patient did not obtain any ONS due to organisational problems. In CG, nine patients received ONS (prescribed by the physician) independently of the 75 % intervention algorithm. One patient showed a contraindication for standard ONS and 56 did not receive ONS. Compliance was analysed for standard ONS only. In all patients receiving standard ONS (both in CG and IG), ONS supplied 10 % of the energy and 15 % of the protein. Thereby, only half of the volume which was prescribed was consumed (median (minimum-maximum): 51 %, 0-100 %). There were 40 % of the patients taking less than one quarter. 9 % took 25 to 49 %, 16 % consumed 50 to 74 % and 35 % finished three quarters or more. Patients' compliance scores (see methods) were as follows: score 1 (low compliance): 27 %, 2: 15 %, 3: 16 %, 4: 25 %, 5 (high compliance): 18 %. Median compliance score was 3 (1-5). This score correlated with the consumed volume ($r=0.94$; $p<0.001$). Comparing the patients with a high ONS compliance to those with low compliance (ignoring randomisation pattern) there were no differences in the major outcome variables (i.e. body weight, difference in body weight, complications, antibiotic therapies, quality of life, re-hospitalisation within six months and death during and six months after hospitalisation). However, the patients who consumed at least half of the ONS showed a trend towards a higher kcal intake compared with the patients with low ONS compliance (1609 (355) kcal vs. 1429 (396) kcal, $p=0.052$). A significant difference was found regarding the ascorbic acid plasma levels at discharge (50.9 (21.7) μmol/l vs. 39.3 (31.0) μmol/l, $p=0.023$) and the mean daily protein intake (71.6 (16.6) g vs. 57.2 (17.4) g, $p<0.001$). Also, the compliance score (4.2 (0.7) vs. 1.6 (0.7), $p<0.001$) and the ONS volume that was consumed (83 (17) % vs. 17(14) %, $p<0.001$) differed between groups. Except for the afternoon and bedtime snack there were no differences concerning energy and protein intake at every meal. Since ONS were served at snack time basically, patients taking less than 50 % of ONS had lower intakes at in-between meals.

5.6 The nutritional status

5.6.1 The developement of the body weight

The body weight and the BMI at discharge were similar between groups (table 5.9). Considering weight change (from ward admission to discharge), patients of IG were able to keep their body weight (admission: 68.1 (16.9) kg vs. discharge: 68.1 (15.9) kg, $p=0.967$) in contrast to CG patients (admission: 66.1 (16.2) kg vs. discharge: 64.7 (16.0) kg, $p=0.002$). Thus, a significant difference in weight change was observed between groups(CG: -1.4 (3.2) kg, IG: 0.0 (2.9) kg; $p=0.008$; table 5.9).

5.6.2 The developement of micronutrient serum parameters

Serum parameters of ascorbic acid, glutathione and 25-OH-D_3 showed different patterns (table 5.8). At discharge, ascorbic acid plasma levels were higher in IG (46.7 (26.7) μmol/l) than in CG (34.1 (24.2) μmol/l, p=0.006) due to a larger increase (+12 μmol/l vs. +7 μmol/l) over time. With respect to glutathione an intervention effect was not visible. Compared to admission, discharge levels were unchanged (IG: 3.94 (1.89) μmol/l vs. 3.69 (2.16) μmol/l, p=0.407). Similarly, 25-OH-D_3 admission levels repeated at discharge with almost the same group difference (IG: 51.4 (24.2) nmol/l vs. CG: 44.4 (26.4) nmol/l, p=0.017). Applying these analyses to the subgroups without supplementation, i.e. without ascorbic acid, 25-OH-D_3 or other vitamins supplementation (s.o.), results were the same. Referring to references for healthy people there were fewer patients with low plasma levels for ascorbic acid at discharge (i.e. 23 %; 27/115) and a trend for a difference between groups existed (IG: 10/61 vs. CG: 17/54, p=0.078). With 25-OH-D_3, 14 % (16/115) of patients had low plasma concentrations (IG: 4/60 vs. CG: 12/55, p=0.029). Referring to the 75 nmol/l reference, even 86 % (99/115) showed low 25-OH-D_3 concentrations (IG: 52/60 vs. CG: 47/55, p=1.000). Low glutathione concentrations affected 28 % (32/114) of the patients at discharge (no group difference). A seasonal influence of UV-B radiation in sun light on vitamin D production was not observed between patients' blood drawn from September to March and April to August.

Table 5.8: Number of patients with micronutrient concentrations below references for healthy people (discharge)

Micronutrient	<Reference IG[2]	<Reference CG[2]	Significance
Ascorbic acid[5]	10/61	17/54	0.078
25-OH-D_3[3]	4/60	12/55	0.029
25-OH-D_3[4]	52/60	47/55	1.000
Glutathione[6]	14/60	18/54	0.298

[1] Control Group
[2] Intervention Group
[3] 25-Hydroxycholecalciferol, reference level: 25 nmol/l
[4] Reference level: 75 nmol/l
[5] Reference level: 17 μmol/l
[6] Reference level: 2.2 μmol/l

5.7 The SF-36 quality of life at discharge

Two physical scales (the physical function subscale (CG:36 (26) %, IG: 51 (26) %) and the physical summary component (CG: 32 (9) %, IG: 37 (11) %)) of the quality of life SF-36 score showed significant differences between groups at discharge (for details refer

to figure 5.5 and table A.3). Additionally, one subscale showed a trend in differences, i.e. the second subscale (role-physical). All of the differences had clinical significance, since a clinically relevant effect size was defined as a minimum difference of five percent. All scales related to mental health did not show any differences between groups.

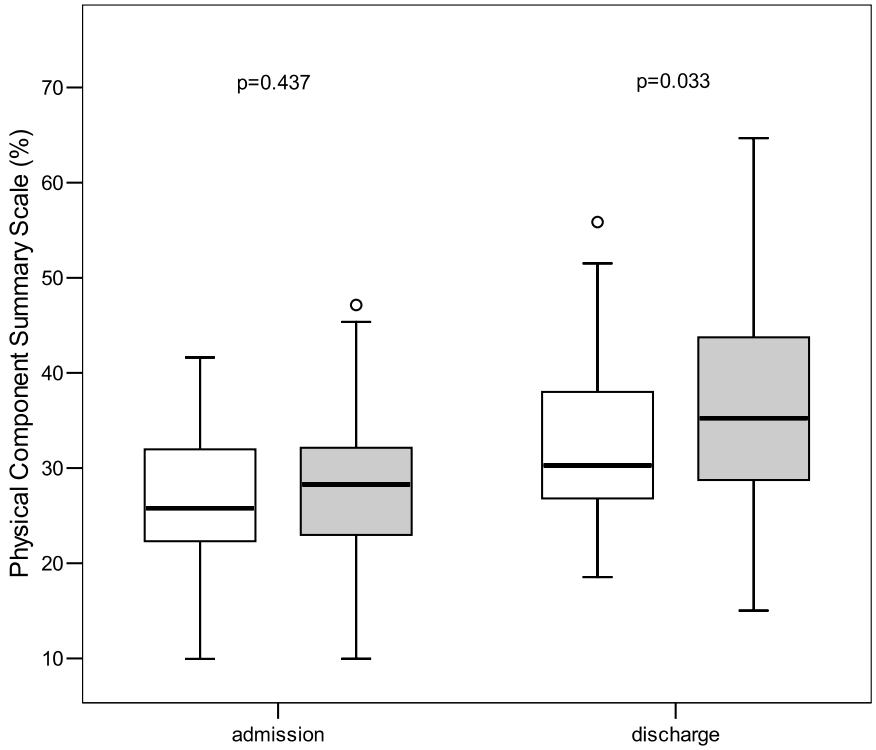


Figure 5.5: SF-36 Physical Component Summary

5.8 Morbidity and Mortality during hospitalisation and follow-up

The number of patients suffering from in-hospital complications was lower in IG than in CG (4/66 vs. 13/66, p=0.035). Complications in IG were infections of unknown aetiology (n=2), urinary track infection (1) and decompensate congestive heart failure (1). In CG complications were: urinary track infection (5), septic arthritis (1), decubitus (1), diarrhoea (1), myocardial infarction (2), decompensated congestive heart failure (1), thrombosis (1) and cerebrovascular ischemia (1). Consequently, antibiotics for the treatment of infectious complications were more often prescribed to patients of CG than IG (IG: 1/66 vs. CG: 8/66; p=0.033). After a censoring for death (i.e. the same analysis without patients who died during hospitalisation), the number of complications and antibiotics only showed trends in differences. In IG, 4 of 64 and in CG 10 of 61 patients had complications (p=0.092). Antibiotics were prescribed to 1 of 64 patients

(IG) and 6 of 61 (CG, p=0.058). Neither length of ward stay (possible (LOS_g) and definite (LOS_h), respectively) nor length of hospital stay (LOS_i) differed between groups (table 5.9). Six months after discharge patients of CG were more often re-hospitalised than patients of IG (IG: 17/64 vs. CG: 28/61, p=0.027). During the study period, seven patients died (5 in CG and 2 in IG, p=0.440). During follow-up, 15 patients died (6/61 in CG and 9/64 in IG; p=0.585).

Table 5.9: Further outcome data

Variable	Randomisation	Mean (SD)	MD (min-max)	Variance	Significance
LOS_g	CG[1]	14.9 (10.2)	13 (4-63)	104.0	0.458
	IG[2]	13.8 (7.1)	12 (3-38)	50.0	
LOS_h	CG	15.9 (10.7)	13 (4-63)	113.5	0.843
	IG	15.7 (9.2)	13 (3-42)	84.1	
LOS_i	C	18.6 (17.1)	14 (4-120)	293.5	0.913
	IG	17.0 (10.4)	13 (3-48)	107.4	
Body weight	CG	64.7 (16.0)	62.2 (29.6-99.9)	256.9	0.227
	IG	68.1 (15.9)	66.0 (41.6-109.9)	252.2	
Difference body weight	CG	-1.4 (3.2)	-0.8 (-13.5-4.8)	10.2	0.008
	IG	0.0 (2.9)	0.0 (-9.1-7.4)	8.4	
BMI[3]	CG	23.6 (4.9)	23.4 (13.2-42.7)	24.4	0.147
	IG	24.6 (4.9)	24.5 (16.3-36.7)	23.9	

[g] Ward admission to possible discharge
[h] Ward admission to definite discharge
[i] Hospital admission to discharge
[1] Control Group
[2] Intervention Group
[3] Body Mass Index

5.9 Per-Protocol analysis

Data was analysed according to ”Per Protocol” as well and revealed no differences in outcome parameters in comparison to the Intention-To-Treat analysis (see appendices A.5).

6 Discussion

The following chapter summarises the main results of the study and compares them to results of similar investigations. The scope of the results is discussed in the light of study limitations. Finally, conditions are specified under which the implementation of our study strategy might be especially successful.

6.1 Main results of this study in the light of current evidence

This study strongly confirms that an individual nutritional intervention, even during a short-term stay, can improve the outcome in hospitalised patients already malnourished or at risk to develop malnutrition in a general medical ward. Since the study design was based on a decisive algorithm (15 % increased calorie intake) and the nurses and physicians of the ward were not informed about group allocation, the beneficial effects on body weight change, complication incidence, antibiotic description, quality of life and ascorbic acid plasma concentration are due to an increased macronutrient (energy) and micronutrient intake. Additionally, the findings support the malnutrition screening by NRS-2002 in general medical wards as it selected the patients who profited from nutritional support in our study.

6.1.1 Multi-factorial nutritional support in other investigations

In three previous intervention studies an individual multi-factorial intervention was less effective than our clinical trial with respect to patient outcome. Hickson et al. [201, 278] designed a randomised controlled mono-centre trial with the aim of investigating the effect of nutritional interventions on nutritional status (BMI, body weight, mid arm (muscle) circumference, triceps skin fold), infection rate, fluid and antibiotics use, functionality (Barthel Score, hand grip strength), plasma albumin, LOS and mortality rate. 592 general medical patients being 65 years and older and unspecific in terms of nutritional risk were randomised to either standard care or additional nutritional support. Interventions (limited to lunch and dinner servings) were conducted by a health care assistant (additionally to ward staff) on each of three different wards during five days a week. The assistants were taught in nutritional care before the start of the study. The study design focused on optimizing nutritional intake. Interventions included individual feeding support, motivation to eat, monitoring intake, solving feeding problems, offering additional snacks and drinks. Details with respect to nutritive measures and individual care were not given. Both, the energy (1288 kcal vs. 1376 kcal, p=0.53) and protein intake (47 vs. 50 g, p=0.62) were numerically higher in IG. This difference was, however, not significant. All primary goals were the same in the two groups. Patients in IG

depended fewer days on intravenous antibiotics (p=0.007) but information on disease severity was not given.

Johansen et al. [198] investigated 212 internal and surgical patients (mean age 62 years, malnourished according to NRS-2002) in a randomised controlled multi-centre study. The intervention measures were performed and guaranteed by a team of a nurse and a dietician at each hospital and included: motivation of staff and patient to follow eating behaviour, adjustment of a nutritional plan on estimates of daily energy and protein needs, and recording of 24h-dietary intake. The results revealed that 62 % of patients of the intervention group and 36 % of the control group covered 75 % or more of their estimated energy requirements. In our study energy coverage of at least 75 % was achieved by 83 % of IG patients. In CG 30 % of the patients managed to reach the 75 % target or more of their individual energy requirements. Regarding outcome parameters body weight change did not differ between groups (-0.22 (0.54) kg vs. 0.10 (0.31) kg) in the Johansen study. In contrast, we detected a significant 1.4 kg loss of body weight in CG patients compared to IG patients. Therefore, weight change still seems to be a marker of the nutritional status although one has to allow for patients with cardiac heart failure. In the present study 37 % of all patients (no difference between groups) lost body weight due to diuretics therapy of hyperhydration. Johansen et al. published a general LOS (mean (SE): 17 (2) vs. 22 (2) days, p=0.028) and a specific LOS_{NDI} (LOS Nutritional Discharge Index; 14 (2) vs. 20 (2) days, p=0.015), which were significantly different only in the subgroup of patients with complications. The LOS in our study was longer in CG compared to IG but without any significant difference. In comparison to other studies the LOS reported here is rather short [121]. If there had been an effect, the number of patients would have been too low to show it. However, our findings agree well with the study of Johansen et al., who reported a difference of LOS of one day in the total study population. Since there were too few patients with complications in our study, LOS was not analysed in this subgroup. Furthermore, Johansen et al. showed no effect on the quality of life according to SF-36. In malnourished out-patients (defined by SGA) QoL improved significantly [152]. In malnourished surgical patients QoL improved significantly in the intervention group who received oral supplements [279]. Equally, the SF-36 scales related to function improved clinically relevant, i.e. a minimum 5 % change, in IG patients in our study. Functionality is a parameter which is affected by nutritional deficiencies early [111]. On the other hand it reacts quickly to the reversion of a depleted status [173]. As a better functionality was related to a higher degree of fat-free mass [280], we assume that the conservation of body weight in our study was at least partly due to the conservation of fat free mass.

The third study by Duncan et al. [199] investigated whether the support by dietetic assistants improved the energy and protein intake and subsequently the nutritional status, LOS, complication rate and the mortality in hip fracture patients. 318 women aged 65 years and older were randomised to either standard or additional care by dietetic assistants. Both groups received oral nutritional supplements. The interventions consisted of checking food preferences, co-ordinating appropriate meal orders, ordering ONS, providing feeding aids, assisting and encouraging during feeding and support of the specialist

dietetic assistants. A detailed feeding algorithm was not available. The energy intake in the "assistants group" was higher than with standard care (1105 kcal/day vs. 756 kcal/day, $p<0.001$). In contrast to our interventions, normal hospital food intake was not significantly higher in the "assistants group". However, the difference in the total daily energy intake was due to a higher ONS intake (409 kcal/day vs. 123 kcal/day, $p<0.001$). Moreover, the decline of mid arm circumference was significantly less in the "assistants group" (-0.89 cm vs. -1.28 cm, $p=0.002$). However, complication rate, LOS, body weight, triceps skin fold and serum parameters (serum albumin, haemoglobin, lymphocyte count) did not differ between the groups. This is partly in contrast to our results - probably due to a different study population and a lower mean total energy intake. We observed a significantly higher number of new complications among those infectious, which were more often treated with antibiotics in CG than in IG. Complications might have fatal consequences [281]. Also, our study did not aim at showing causal relations between the severity of complications and mortality. However, the number of patients with complications was no more statistically different after the data had been censored for death. Besides, readmission rates within six months were twice as high in CG than in IG. Twenty-eight out of 61 patients (46 %) in CG and 17 out of 64 patients in IG (27 %) were re-hospitalised. This agrees with studies in the ambulant setting [173, 131]. Duncan et al. reported fewer deaths in both the trauma unit (10.1 % vs. 4.1 %, $p=0.048$) and at 4 months after discharge (22.9 % vs. 13.1 %, $p=0.036$) while hospital mortality did not differ significantly. There was no difference between groups in either period of time, i.e. within hospitalisation and during follow-up, in our study. This applies to most studies since a causal relationship was rarely reported. [179, 282, 283]. However, some studies show an effect of nutritional support on mortality. There, the intervention periods were mostly longer [188, 284, 285] and patients were more seriously ill than those in our study [286].

6.1.2 Intervention efficiency in different study settings

As shown above, the influence of nutritional support on the outcome is still inconsistent. The different levels of intervention efficiency may explain these differences. It has been shown for cystic fibrosis patients that outcome improves dependent on the extent of energy delivery [287]. In contrast, it is not easy to provide patients with the complete and effective intervention [200, 288]. A tight feeding algorithm as applied in our study may thus be beneficial in order to achieve a high feeding quality and efficiency. Furthermore, we designed our study to avoid much heterogeneity in order to facilitate the detection of differences in the outcome. We limited heterogeneity of both the patient group considered (only medical patients), the setting (one hospital, one ward) and the interventions (one person applying the nutritional support, similar amount of personal attendance in both groups). The interventions were further limited to patients who were most likely to profit from nutritional support (i.e. patients being at risk of malnutrition according to NRS-2002 and not having the manifested disease yet; exclusion of terminal patients).

As indicated in table 6.1 the study settings of the above cited intervention studies vary. The studies by Hickson and Frost [289] was the largest of these studies but did not

reach the minimum effect size of the nutritional intervention. Additionally, although the elderly are especially at risk of malnutrition, risk patients were not defined. The study by Johansen et al. [198] probably had too much statistical noise to elucidate more outcome differences. As patients in three hospitals with different specialities were recruited and 6 persons were applying the intervention, the study setting may have been to heterogenous. The study by Duncan et al. [199] was performed at one study ward by two dieticians. Besides, more than 300 patients were recruited (which may have complicated a more successful intervention). In spite of that, the study setting was more homogenous than with Hickson et al. or Johansen et al. Additionally, the study patients (operated at a trauma ward) may have been more prone to nutritional support due to more severe illness which may be the reason for the improved mortality rate in the intervention group.

Table 6.1: Key parameters of multifactorial nutritional intervention trials

Parameter	Hickson et al.	Johansen et al.	Duncan et al.	Starke et al.
No. of wards/ hospitals	3/1	3/3	1/1	1/1
Departments	medical for elderly	surgical and medical	trauma (hip fracture)	medical
No. of patients	592	212	318[1]	132
Mean age	82	62	84	72
Nutritional status	not specified	NRS-2002≥3	not specified	NRS-2002≥3
Intervention performer	3	3x2	2	1
Effect size energy	n.s.	285 kcal/d	349 kcal/d	438 kcal/d
Effect size protein	n.s.	11.5 g/d	-	21.5 g/d
Mean energy intake IG/CG	23/22 kcal/kg	30/25 kcal/kg	19/13 kcal/kg[3]	24/18 kcal/kg
Mean protein intake IG/CG	0.8/0.8 g/kg	1.1/0.9 g/kg	-	1.0/0.7 g/kg
Improved Outcome[2]	n.s.	LOS (complication)	MUAC, mortality	Body weight change, QoL, complications, antibiotic therapies, readmissions

[1] women only, [2] all ITT analysis, [3] third post-operative day

Unfortunately, the cited studies did not describe details of the nutritional intervention proceedings. Hickson et al. reported a difference in the energy intake of 88 kcal/d, which

might be too low to show any effect on the outcome. Either the educated assistants were not trained enough, or it was insufficient to employ them only during the week or elderly patients do not respond to nutritional interventions. Additionlly, the standard energy intake (i.e. the energy intake of CG) was close to normal, which complicated a significant intervention effect. Johansen et al. reached the difference we intended to achieve, i.e. about 285 kcal/d (see power calculation). This amount seems to be the minimum difference related to a change in outcome parameters according to the literature [15]. However, Duncan et al. reported a difference (349 kcal/d) which was above this minimum and due to a higher ONS consumption. With 438 kcal/d the difference achieved in our study was even higher and normal food contributed to the largest part of energy and protein intake. Protein values were often reported in relation to the energy intake. A quite small difference with Hickson et al. (3g/d) was surpassed by Johansen et al. (11.5 g/d). The difference in the present study amounted to 21.5 g/d. However, the energy percentage presented by protein intake was similar in all studies, i.e. 16 % to 18 %.

6.1.3 Food compounds possibly involved in the conservation of nutritional status

The main proportion of energy and protein was delivered by normal food in both of our study groups. In IG, ONS only covered a low percentage of energy and protein because of a low compliance. Food fortification often has limitations due to the amount of maltodextrin, protein powder or oil that is miscible with normal food. It also played a minor role in our study. A better option to increase food intake is the supply of in-between snacks since patients often wrangle with portion sizes. Up to 25 % of the daily energy was supplied by these snacks in former studies [290] which was similar to our results (i.e. 27 %). However, it was difficult to attribute the effects on outcome to one or more of the food components, i.e. macronutrients and/or the group of micronutrients and/or energy per se as will be discussed in the next section.

The role of macronutrients and energy

The development of body weight is mainly influenced by the intake of energy per se. Adiposity research has demonstrated that the amount of energy and not the macronutrient distribution is responsible for weight gain or loss [291]. A low energy intake, i.e. less than 75 % of the individual TEE, was associated with weight loss in hospitalised patients [72]. Hypermetabolism induced by the disease may require more total daily energy. Especially, an accelerated protein turnover and muscle breakdown have been described [98] which might be stopped or reversed by a sufficient protein intake. In contrast, protein can inhibit the appetite, which may be counterproductive in malnourished patients [292, 293]. Whether the quantity of protein is important without the relevant amount of calories is discussed vehemently especially when referring to hunger or catabolic conditions [260, 261]. Additionally, fat-free mass is an important predictor of REE. Thus, the success of nutritional interventions might depend on the extent of

disease-related cachexia or age-related sarcopenia apart from age and disease itself.

The role of micronutrients

The risk of developing multiple micronutrient deficiencies is high both with age and during disease [294, 295]. Thus, the impact of multiple micronutrient deficiencies on immunity was most obvious in infectious complications [296]. A lack of energy and protein is accompanied by a deficit in micronutrients [294] especially when total food intake is decreased. At admission one third of our patients (43/132) showed ascorbic acid values below the reference level of healthy people (17 μmol/l). Referring to 25-OH-D_3 (25 nmol/l), 12 % (16/132) and to glutathione (2.2 μmol/l) one quarter (33/132) of the patients had low levels (no differences between groups). Referring to a 25-OH-D_3 level of 75 nmol/l [297], 86 % (114/132) of the patients had lower levels at admission. The high prevalence of 25-OH-D_3 deficiency is in line with a publication showing that 25-OH-D_3 deficiencies have been related to several disease conditions apart from the bone metabolism [298]. Besides, the precursor skin production is reduced in the elderly. Additionally, both the elderly [299] and the ill [300] are less mobile and often home-bound supporting the high deficiency prevalence that was found in the present study. As oral food intake contributes only little to the body's 25-OH-D_3 content it is not surprising that no intervention effect was observed. Even with 17 % of the patients who received vitamin D treatment (i.e. 400 I.U./d) no effect on plasma levels was recorded. This is probably due to the low doses (half as much of what is recommended). An amount of 400 I.U. was recorded to raise plasma levels by 5 to 10 nmol/l, which agrees with our analyses in supplemented patients (results not shown).

The deficiency prevalence was low regarding vitamin C and its measurable metabolites ((mono-) dehydro) ascorbic acid. In serum levels the reduced metabolite dominates [301]. Likewise, the reduced metabolite is decreased during disease and age in favour of its oxidative equivalent [302, 303, 304]. Since fresh fruit is available all year round it is easy to keep a balanced ascorbic acid serum concentration. Nevertheless, serum levels may react quickly to a decreased or interrupted supply as well as to replenishment in a deficiency condition [305]. How the active replenishment with single micronutrients in the hospital setting affects the outcome is mainly unclear. One study showed that early administration of ascorbic acid and α-tocopherol reduced organ failure and LOS in ICU in critically ill patients [306]. The intervention effect on ascorbic acid levels may thus have contributed to the better outcome in our study.

The tripeptid glutathione is involved in many processes during both normal and disease metabolism [307]. Its main task is to keep a stable level of reduced metabolites and the balancing of redox processes in the metabolism. Therefore, it interacts with many other components and molecules, e.g. antioxidants [308]. Its precursors i.e. glutamine and cysteine obtained importance as they limited glutathione synthesis especially in critically ill patients [309]. Thus, an influence of amino acid intake on glutathione synthesis might be possible as has been shown with healthy people during adaption to a lower protein intake, i.e. a negative nitrogen balance [310]. However, an intervention effect with the present study population has not been observed.

In our study food quality was chosen to be high. For instance, in-between meals combined a micronutrient source (e.g. fruit salad) and protein- and energy-dense components (e.g. full cream yoghurt). The advantages related to "normal complete food" have not been much investigated until now. However, there is knowledge from other nutritional sectors. The health effect of fruits and vegetables was not validated by the intake of artificial vitamins [311, 312, 313]. Another example is the advantage of breast-milk compared to bottled milk [314]. The concerted action of micronutrients (e.g. thiamine) and proteins (e.g. transketolase [315]) in energy metabolism underlines the importance of a sufficient intake of both micronutrients and macronutrients. Natural food may thus be beneficial because of an optimal ratio of all compounds. In addition, they contain immuno- and antioxidatively active compounds (e.g. secondary plant micronutrients) which are not available in designed food or even unknown up to now.

Since ascorbic acid serum concentrations have been influenced by our interventions other micronutrient concentrations (which we did not analyse) may have been affected as well. Therefore, the increased micronutrient concentrations may have contributed to the outcome benefits beside the mere effect of a higher caloric and protein intake. Recently a British study showed that ONS increased vitamin serum levels in comparison to "low-quality" snacks (e.g. puddings, biscuits etc. [188]). In the group supplemented with ONS (in that study the more valuable nutrient source) even fewer complications were recorded [188]. The quality of food may hence be important apart from food quantity.

6.2 Limitations of the study

Our results have to be interpreted in light of some limitations related to the design of our study. We decided not to exclude patients at malnutrition risk sharing a room with a patient randomised to the opposite study arm because of limited human resources. However, this situation occurred only five times. These patients were easily treated according to the study protocol as they did not interact. Therefore, we assume that they did not influence each other although we can't prove that. Additionally, patients sharing a room might not have negatively influence our study in terms of a "Good Clinical Practice" since a CG patient might have been influenced to eat more or an IG patient to eat less. In both cases, however, our intake difference would have been less thus reducing the chance of observing a difference in the outcome. Additionally, personal attendance might lead to higher food intake. Hence, we tried to balance personal attendance in the study groups although we did not measure attendance time. The mental scales of the SF-36, however, may be a surrogate parameter describing the influence of personal attendance [316]. They did not differ between groups.

There were more female but younger patients in IG. Although these differences were not statistically significant they should be considered as a heterogeneous study group decreases the chance of finding small differences. Females eat less than men [317] and older people eat less than younger people [105]. The effect on the intervention - if any - might therefore be balanced.

The main limitations of our study are connected to the study power. Preferred outcome parameters like morbidity (including hospital-acquired complications), LOS, quality of life or mortality are often influenced by other factors than nutrition alone. Therefore, interventions in large trials, e.g. multicentre studies, are needed to confirm relevant differences between nutritional support and standard care. However, a large randomised controlled trial complicates intervention homogeneity and the detection of causal relations. Whether randomised controlled intervention trials only shall be considered the "gold standard" in order to investigate causal relations between nutrition and the outcome is questioned and discussed elsewhere [318, 19, 269, 319]. Although the difference in complication incidence is significant (p=0.035), our study was not powered to statistically confirm a causal relation to nutritional intervention. However, other causes to explain the differences were hard to define.

6.3 Relevance of the results for the practical implementation

The results of our study apply to patients with a malnutrition risk according to the NRS-2002 only. Whether different screening or assessment tools show similar results is a question of future research. In addition, the question whether the NRS-2002 selects patients who profit of nutritional support in different (e.g. surgical) departments remains to be investigated. Our experience with the application of only the NRS-2002 main screening was however convincing to recommend its use. All but 6 of 767 patients admitted to the study ward could be screened showing its wide range of application.

In sum, our results are promising but may not be readily transferable to different hospitals. The medical clinic in Liestal, although belonging to the university hospital Basel, is rather a secondary care hospital. Especially hospitals of tertiary care (i.e. university hospitals) may need different strategies due to higher diagnostic and treatment frequency. Additionally, malnutrition prevalence rates may be higher due to more severe diseases and frequent readmissions requiring more human resources than in our study. However, the decentralised ward-based nutritional support as applied in our study may be especially fruitful in big hospitals.

An advantage for the intervention performance was the in-house kitchen of the hospital. In contrast to extern meal delivery services, the kitchen produced high quality fresh food and individualised orders were responded to most of the time. Small cakes or biscuits in plastic packages (a common snack in big hospitals or with extern meal deliverers) were avoided. Instead, fresh yoghurt, creams or even ice cream with fruit salad were stored on the ward fridge and finally prepared and offered when the patient was ready to eat. All food items were standardised available and delivered by the hospital kitchen. Also, main meals were stored on the ward in case a patient was absent at meal time. As soon as the patient was allowed to eat the meal was heated and offered. During the study the standard menu ordering system was used in order to not increase the work load for the kitchen. However, the kitchen staff was always available and open in case of a few special orders, questions related to ingredients or when food was missing and needed to be replaced. Additionally, the limited hospital size (399 beds) simplified

organisational issues and communication. On the ward, physicians, (head) nurses and therapists were always open to questions or comments on the treatment.

7 Conclusion and Outline

Our findings responded to the question whether nutritional support on an individual basis is efficient during hospitalisation. Moreover, a couple of new question arose while performing the study.

7.1 Conclusion

Medical patients at malnutrition risk profit from nutritional support even during short hospitalisation periods. They maintain their nutritional status indicated by a stable body weight and higher concentrations of serum ascorbic acid levels. The functionality-related quality of life at discharge is better in patients receiving nutritional support in contrast to risk patients receiving standard care. The incidence of complications and subsequent antibiotic treatments during hospitalisation were reduced in patients receiving nutritional support. Additionally, the rehospitalisation rate was only half as high in IG compared to standard care patients. The NRS-2002 screening was an appropriate tool to identify those patients who finally profited from nutritional support and can thus be recommended. We assume that nutritional care has to follow a tight algorithm in order to guarantee that the daily individual needs of energy and protein are covered. The evaluation of the actual amount of food that is consumed by the patients is necessary in order to adjust the nutrition on a short-term basis. It appears to be an advantage that the person responsible for the nutritional support is based on the ward.

7.2 Outline and future research

Although the replication of our findings especially in larger settings may be of importance, there are some ideas which may be the basis for further trials.

- The developers of the NRS-2002 observed that about one fourth of the patients were misclassified. In our study, there were also a considerable number of patients who managed to take enough food in the control group. Thus, they were not reliant on nutritional support although a risk was detected according to NRS-2002. Future studies may take this into account in order to define patients who actually profit from nutritional support more precisely.
- For practical reasons the NRS-2002 main screening may be sufficient to select patients at malnutrition risk. Probably, the main screening takes not much more time than the pre-screening. Additionally, it only specifies the pre-screening without

adding additional information. Then, skipping the pre-screening would probably safe some time in wards with moderate to high malnutrition prevalence rates.

- Whether the NRS-2002 selects patients of e.g. surgical or geriatric departments remains to be investigated.

- We defined the intervention targets by estimating the individual TEE. The estimates were, however, significantly higher than the actual daily intakes. Studies in need for the exact TEE should therefore apply indirect calorimetry and not rely on regress equations. For intervention studies evaluating the daily food intake this estimate may still be adequate as the absolute difference to the actual intake was low even though it was significant (i.e. 175 kcal in IG).

- 14 % of the patients in each group (8 of 66) were included during hospitalisation. This is of disadvantage for the intervention effect because early interventions may be more effective. For research reasons one may exclude those patients in order to quantify the intervention effect more precisely. However, as our study setting reflects the real situation, we were able to show the efficiency under these circumstances and thus practicability.

- We assume that the composition of natural food compounds, i.e. macronutrients in combination with micronutrients is of advantage in malnutrition since most of the energy and protein was supplied by normal food. In order to identify the most potent nutrient families or a combination of them influencing the nutritional status, more investigations are necessary focussing on the comparison of, for example, micronutrient-rich vs. micronutrient-poor food compounds. Additionally, the protein level may be changed (e.g. protein-rich vs. protein-poor). Most interesting would be a comparison of natural food to artificial supplements. Besides, a definiton of food items that are favoured by the patients can be interesting. Our experience supports the use of easy-to-swallow fresh fruity food, i.e. joghurt, curd cheese or ice cream with saisonal fruits and cream. However, we did not analyse objective data so far.

- Additionally, not only different nutritional strategies but also nutritional support vs. medical treatment needs to be explored especially considering the patients' quality of life. The importance of nutrition especially during a treatment may thus be highlighted.

- In order to gain evidence related to morbidity and mortality multi-centre studies with large study populations are needed. Such an approach, however, may need well-trained and experienced investigators performing the intervention in order to achieve the necessary intervention efficiency.

- Finally, the cost-effectiveness of nutritional support may be of economic interest. Especially the influence of natural food interests because of its low expense in comparision to other treatments. Additionally, the possible role of a nutritionist on

each ward with, for example, high malnutrition prevalence rates may be discussed since individualised services are connected to human resources. The ward-based nutritional support may also be compared to the so far common nutrition teams which are responsible for a whole hospital, often occupied with ambulant dietary counselling and less well-integrated in the medical operations and structures than physicians or nurses.

8 Summary

Malnutrition continues to be a relevant health-care problem accompanying disease and age. High prevalence rates are especially found among hospitalised patients. Meanwhile, there is ample evidence that an insufficient nutritional status limits a positive clinical as well as economical outcome. However, there is still need for intervention studies investigating causal relations. Additionally, the implementation of nutritional strategies to treat malnutrition in the hospital setting is a challenge. Therefore, a randomised controlled intervention study was performed with the aim to develop and evaluate a routinely manageable concept for an improved nutritional care of malnourished in-hospital patients.

This study was performed from January 2007 to November 2007 (follow-up until June 2008) until 132 adult patients with a Nutritional Risk Screening (NRS-2002)$\geq$3 were recruited. Patients with the following conditions were excluded: no I.C., a terminal condition, an expected stay less than 5 days, previously participating in the study, being on dialysis, starvation and parenteral nutrition. Patients were randomised to the intervention (IG) or control group (CG) and thus received either an individual nutritional support for 5 to maximum 28 days or standard care. The nutritional support comprised a detailed nutritional assessment, individual food ordering, the visually evaluation of food intake, food fortifications, in-between snacks, oral nutritional supplements (ONS) and solving eating problems. Primary endpoints of the study were the mean daily energy and protein intakes. The change in body weight during hospitalisation, the number of complications, the number of antibiotic therapies due to infectious complication, the length of stay, the quality of life according to the SF-36 questionnaire, the readmission and the mortality rates were considered as secondary endpoints. Additionally, plasma concentrations of 25-OH-D_3, ascorbic acid and glutathione were evaluated. Except of the energy and protein intake all outcome data were blinded in terms of that physicians and nurses who were responsible for the outcome did not have access to group allocation.

The overall malnutrition prevalence on the study ward was 32%. All study data was analysed according to the intention to treat principle. The baseline data was equally distributed between the study groups. Repeated measure ANOVA showed a highly significant intervention effect on the energy and protein intake. The mean energy intake was higher in IG (1553 (341) kcal/d) than in CG (1115 (381), $p<0.001$). The same applies to the mean protein intake (65.4 (16.4) g/d vs. 43.9 (17.2) g/d, $p<0.001$). 55 patients (i.e. 83%) in IG and 20 (i.e. 30%) in CG covered 75% or more of their individual estimated TEE. The main coverage of energy was achieved by normal food (IG: 86 (9)%, CG: 95 (11)%, $p<0.001$). Likewise, protein intake was primarily covered by normal food (IG: 82 (12)%, CG: 96 (12)%, $p<0.001$). Protein contributed to energy supply by 18 (2) and 17 (3)% ($p=0.008$) in IG and CG, respectively.

All patients in IG had at least one meal during hospitalisation which was consumed less than 75%. In-between meals and ONS were therefore offered. ONS covered 9 (8)% of energy intake and 13 (11)% of protein intake in IG. In CG ONS covered 2 (8) % of energy and 3 (11)% of protein ($p<0.001$ between groups). Overall compliance of ONS intake was 51% and only 35% of the patients took more than three quarters of the ONS drinks. However, if ONS consumption was successfully, then daily total protein needs were easier met. In contrast, main outcome parameters (like body weight change, complication incidence, LOS and QoL) did not differ between patients consuming less and more than half of the ONS, respectively. In-between meals contributed to energy intake by 27 (8)% (IG) and 11 (10)% (CG, $p<0.001$). Similarly, in IG 27 (10)% and in CG 9 (12)% of the daily protein was covered by in-between meals ($p<0.001$). The energy and protein intake was significantly different between groups at all meals except for breakfast and a trend-like difference only at supper. Apart from in-between meals and ONS, food fortification, enteral nutrition and intravenous supply were applied but did not contribute considerably to neither energy nor protein intake.

The nutritional status of IG patients was affected by the interventions. A loss of body weight was recorded in CG patients (-1.4 (3.2) kg) whereas IG patients kept their body weight (0.0 (2.9) kg, $p=0.008$). Additionally, the serum ascorbic acid levels at discharge were higher in IG (46.7 (26.7) μmol/l) than in CG (34.1 (24.2) μmol, $p=0.006$) due to a larger increase over time. In contrast, glutathione and 25-OH-D_3 levels did not change. QoL recorded by the SF-36 questionnaire revealed differences between groups at discharge. IG patients improved clinically relevant (i.e. at least 5%) in comparison to CG patients in the physical summary component (i.e. the summary scale describing functionality) and one subscale related to functionality. Additionally, patients of IG had fewer hospital-acquired complications (4/66 vs. 13/66, $p=0.035$) and needed less antibiotics (1/66 vs. 8/66, $p=0.033$). In contrast, LOS in the ward and the hospital did not differ between groups. The same applies to the mortality during hospitalisation and until 6 months after discharge. However, patients of IG were only half as often re-admitted compared to CG patients during the 6 months of follow-up (17/64 vs. 28/61, $p=0.027$).

In three previous intervention studies an individual multi-factorial intervention was less effective than our clinical trial. Hickson et al. investigated whether health care assistants tought in nutrition, can improve food intake and several outcome parameters in elderly medical patients. Both, the energy and the protein intake were not significantly higher in the "assistants groups". Accordingly, all study endpoints were similar in the two groups. Johansen et al. investigated whether a team of a nurse and a dietician can improve food intake in medical and surgical patients. Both, the energy and the protein intake differed between IG and CG. However, the only outcome parameter that was influence by the intervention was the LOS in a subgroup of patients who had acquired a complication during hospitalisation. Neither the body weight change, the QoL nor the LOS in the total population differed between groups, probably because of a heterogenic study setting. The third study in a trauma ward revealed that dietetic assistants who were additionally employed to support the dieticians, can improve the energy intake,

especially by a higher consumption of ONS. Thus, patients in the "assistants group" showed a smaller decline in the MUAC and a lower mortality rate in the trauma ward and during 4 months of follow up.

Comparing these findings with our trial then the study details reveal that the heterogenic settings and interventions may have disclosed nutritional effects due to much statistical noise. Our trial was planned to avoid much heterogeneity, i.e. there was only one study ward, one intervention performer and only medical patients. Furthermore we achieved a high effect size concerning the energy and protein intake due to a tight feeding algorithm. Additionally, we recruited patients who were most likely to profit from nutritional support, i.e. showing a malnutrition risk according to NRS-2002 (and not the manifested disease necessarily). Moreover, the main proportion of energy and protein was delivered by normal food. Although there is not much evidence related to the type of intervention so far, this might have been an advantage because normal food is complete in all types of nutrients and the compliance is high.

In conclusion, our results are promising and the implementation of this nutritional approach can be recommanded even for larger hospitals as the nutritional support is ward-based.

A Appendices

A.1 Nutritional Risk Screening (Original)

Nutritional Risk Screening (NRS 2002)

Table 1 Initial screening			
1	Is BMI <20.5?	Yes	No
2	Has the patient lost weight within the last 3 months?		
3	Has the patient had a reduced dietary intake in the last week?		
4	Is the patient severely ill ? (e.g. in intensive therapy)		
Yes: If the answer is 'Yes' to any question, the screening in Table 2 is performed. **No**: If the answer is 'No' to all questions, the patient is re-screened at weekly intervals. If the patient e.g. is scheduled for a major operation, a preventive nutritional care plan is considered to avoid the associated risk status.			

Table 2 Final screening			
Impaired nutritional status		**Severity of disease ($\approx$ increase in requirements)**	
Absent **Score 0**	Normal nutritional status	Absent **Score 0**	Normal nutritional requirements
Mild **Score 1**	Wt loss $>5\%$ in 3 mths or Food intake below 50–75% of normal requirement in preceding week	Mild **Score 1**	Hip fracture* Chronic patients, in particular with acute complications: cirrhosis*, COPD*. *Chronic hemodialysis, diabetes, oncology*
Moderate **Score 2**	Wt loss $>5\%$ in 2 mths or BMI 18.5 – 20.5 + impaired general condition or Food intake 25–60% of normal requirement in preceding week	Moderate **Score 2**	Major abdominal surgery* Stroke* *Severe pneumonia, hematologic malignancy*
Severe **Score 3**	Wt loss $>5\%$ in 1 mth ($>15\%$ in 3 mths) or BMI <18.5 + impaired general condition or Food intake 0-25% of normal requirement in preceding week in preceding week.	Severe **Score 3**	Head injury* Bone marrow transplantation* *Intensive care patients (APACHE>10).*
Score:	+	**Score**:	**=Total score**
Age	if ≥ 70 years: add 1 to total score above	**=age-adjusted total score**	
Score $\geq$3: the patient is nutritionally at-risk and a nutritional care plan is initiated **Score $<$3**: weekly rescreening of the patient. If the patient e.g. is scheduled for a major operation, a preventive nutritional care plan is considered to avoid the associated risk status.			

NRS-2002 is based on an interpre-tation of available randomized clinical trials.
*indicates that a trial directly supports the categorization of patients with that diagnosis. Diagnoses shown in *italics* are based on the prototypes given below.
Nutritional risk is defined by the present **nutritional status** and risk of impairment of present status, due to **increased requirements** caused by stress metabolism of the clinical condition.

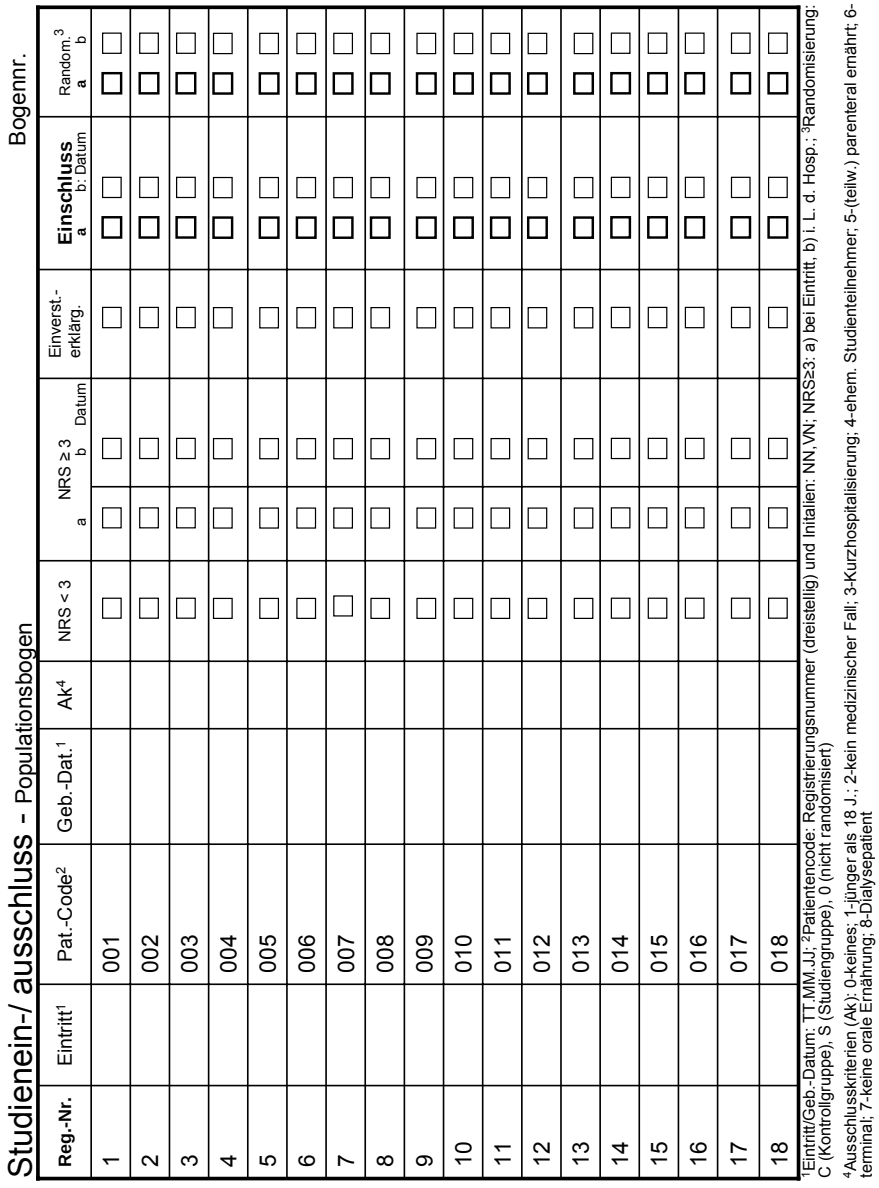
A nutritional care plan is indicated in all patients who are

(1) severely undernourished (score = 3), or (2) severely ill (score = 3), or (3) moderately undernourished + mildly ill (score 2 + 1), or (4) mildly undernourished + moderately ill (score 1 + 2).
Prototypes for severity of disease
Score = 1: a patient with chronic disease, admitted to hospital due to complications. The patient is weak but out of bed regularly. Protein requirement is increased, but can be covered by oral diet or supplements in most cases.
Score = 2: a patient confined to bed due to illness, e.g. following major abdominal surgery. Protein requirement is substantially increased, but can be covered, although artificial feeding is required in many cases.
Score = 3: a patient in intensive care with assisted ventilation etc. Protein requirement is increased and cannot be covered even by artificial feeding. Protein breakdown and nitrogen loss can be significantly attenuated.

Figure A.1: Nutritional Risk Screening 2002 (the Original with the prescreening (not used in the study), the final screening and information on its application

A.2 Study sheets

A.2.1 Recruitment list



Studienein-/ ausschluss - Populationsbogen

Bogennr.

Reg.-Nr.	Eintritt[1]	Pat.-Code[2]	Geb.-Dat.[1]	Ak[4]	NRS < 3	NRS ≥ 3 a	NRS ≥ 3 b Datum	Einverst.-erklärg.	Einschluss a	Einschluss b: Datum	Random.[3] a	Random.[3] b
1		001			☐	☐	☐	☐	☐	☐	☐	☐
2		002			☐	☐	☐	☐	☐	☐	☐	☐
3		003			☐	☐	☐	☐	☐	☐	☐	☐
4		004			☐	☐	☐	☐	☐	☐	☐	☐
5		005			☐	☐	☐	☐	☐	☐	☐	☐
6		006			☐	☐	☐	☐	☐	☐	☐	☐
7		007			☐	☐	☐	☐	☐	☐	☐	☐
8		008			☐	☐	☐	☐	☐	☐	☐	☐
9		009			☐	☐	☐	☐	☐	☐	☐	☐
10		010			☐	☐	☐	☐	☐	☐	☐	☐
11		011			☐	☐	☐	☐	☐	☐	☐	☐
12		012			☐	☐	☐	☐	☐	☐	☐	☐
13		013			☐	☐	☐	☐	☐	☐	☐	☐
14		014			☐	☐	☐	☐	☐	☐	☐	☐
15		015			☐	☐	☐	☐	☐	☐	☐	☐
16		016			☐	☐	☐	☐	☐	☐	☐	☐
17		017			☐	☐	☐	☐	☐	☐	☐	☐
18		018			☐	☐	☐	☐	☐	☐	☐	☐

[1]Eintritt/Geb.-Datum: TT.MM.JJ; [2]Patiententencode: Registrierungsnummer (dreistellig) und Initalien: NN,VN; NRS≥3: a) bei Eintritt, b) i. L. d. Hosp.; [3]Randomisierung: C (Kontrollgruppe), S (Studiengruppe), 0 (nicht randomisiert)

[4]Ausschlusskriterien (Ak): 0-keines; 1-jünger als 18 J.; 2-kein medizinischer Fall; 3-Kurzhospitalisierung; 4-ehem. Studienteilnehmer; 5-(teilw.) parenteral ernährt; 6-terminal; 7-keine orale Ernährung; 8-Dialysepatient

Figure A.2: Recruitment list with the following columns: Reg.-Nr.: Registration number, Eintritt: Date of admission, Pat.-Code: patient registry code, Geb.-Dat.: date of birth, Ak: exclusion criteria, NRS<3: no malnutrition risk, NRS>3: malnutrition risk (a) and date of screening (b), Einverständniserklärung: informed consent, Einschluss: at admission (a), during hospitalisation (b) plus date of inclusion, group allocation at admission (a) or during hospitalisation (b)

A.2.2 NRS-2002 admission

EINTRITT **Pat.-Code:**

Eintrittsdatum: _____ Zi.: _____ Geschlecht: w □ m □

Größe (anam.): _____ Gewicht (anam): _____ Blutabnahme: nein □ ja □

Größe (gem.): _____ Gewicht (gem.): _____ BMI [kg/m²]*: _____

Diagnosen: _____ ICD-10-Code: _____

_____ ICD-10-Code: _____

_____ ICD-10-Code: _____

Medikamente: _____

_____

_____

_____

_____

Störung des Ernährungszustandes (Score I)		**Krankheitsschwere (Score II)**	
Leicht 1 Pkt.	Gewichtsverlust >5%/3 Monaten oder Nahrungszufuhr 50-75% des Bedarfs in der vergangenen Woche	Leicht 1 Pkt.	Schenkelhalsfraktur Chronische Erkrankungen mit Komplikationen: Leberzirrhose, COPD, chronische Hämodialyse, Diabetes, Krebsleiden Radiotherapie
Mittel 2 Pkt.	Gewichtsverlust >5%/2 Monaten oder BMI 18,5-20,5 kg/m² und reduzierter Allgemeinzustand oder Nahrungszufuhr 25-50% des Bedarfs in der vergangenen Woche	Mittel 2 Pkt.	Große Bauchchirurgie Cerebrovaskuläre Insulte Schwere Pneumonie Hämatologische Krebserkrankung Geriatrische Patienten mit langer Hospitalisation Chemotherapie
Schwer 3 Pkt.	Gewichtsverlust >5%/1 Monaten oder BMI <18,5kg/m² und reduzierter Allgemeinzustand oder Nahrungszufuhr 0-25% des Bedarfs in der vergangenen Woche	Schwer 3 Pkt.	Schädel-Hirn-Trauma Polytrauma Schwere Verbrennungen Knochenmarkstransplantation Intensivpflichtige Patienten (APACHE-II>10)
Teilpunktzahl Score I:		Teilpunktzahl Score II:	
Gesamtpunktzahl Score I+II inkl. 1 Alterspunkt (Alter ≥ 70 Jahre):			

Gem.=gemessen; anam.=anamnestisch; Pkt.=Punkt/e; Zi=Zimmer
*nur wenn Gewicht nicht ermittelbar, wird der Oberarmumfang (OAU) in cm angegeben

Figure A.3: Modified NRS-2002 admission sheet

A.2.3 Discharge sheet

AUSTRITT **Pat.-Code:**

Zi.:_____ **Austrittsdatum:**_____ Tod i. Spital: nein ☐ ja ☐ , verlegt: nein ☐ ja ☐

Gewicht (gem.): _____ BMI [kg/m^2]:_____ Blutabnahme nein ☐ ja ☐

Diagnosen: _____ ICD-10-Code:_____

_____ ICD-10-Code:_____

_____ ICD-10-Code:_____

_____ ICD-10-Code:_____

Komplikation:_____

nichtinfektiös _____

_____

_____

	Antibiotika-Therapie
infektiös	

Compliance: 1) keine ☐ 2) schlecht ☐ 3) mittelmäßig ☐ 4) gut ☐ 5) optimal ☐
(Supplement)

Follow Up-Datum:_____

Wiedereintritt: nein ☐ ja ☐ (Dat.:), Tod: nein ☐ ja ☐ (Dat.:)

Figure A.4: Discharge and Follow-Up sheet

A.2.4 Nutritional anamnesis

Ernährungsanamnese – Patientenbogen | Pat.-Code:

Standardgewicht:____kg | Kleidung zu gross ☐

Gewichtsverlust:_____kg/ _Mo | Gewichtsanstieg:_____kg/ _ Mo

Bedarf:	REE:_____ kcal	Aktivitätsfaktor:_____
(Eintritt)		Krankheitsfaktor:_____
	Total:_____kcal/d	**Protein:_____g/d**

Essverhalten Menge, Lieblings-/ vermiedenes Essen, Dauer falls hypokalorisch, Konsistenz, Veränderung zu sonst

Frstk_____

Mittag_____

Abend_____

Sonstiges_____

Medikamente, NEM, sonstige Zusätze

GI-Symptomatik Übelkeit, Diarrhöe, Erbrechen, Dauer, Stuhl, Urin.(KG)

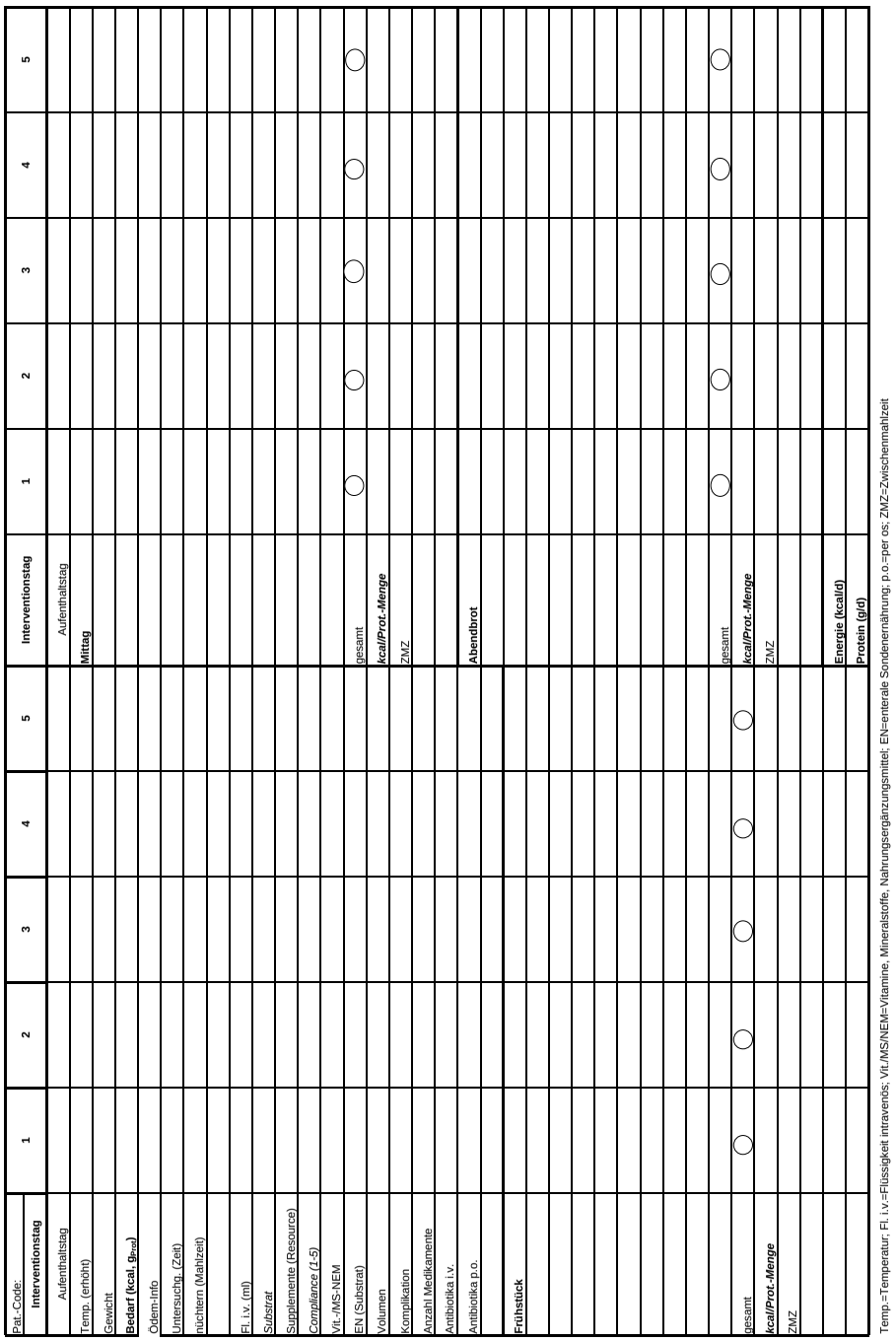
Sonstige Einschränkungen Kauprobleme, Zahnersatz, Dysphagie, Appetitlosigkeit, ...

Leistungsfähigkeit Mobilität, Sturzgefahr, Selbständigkeit, Müdigkeit, Schwäche, Angst,...

Klinisches Bild: Ödeme, Aszites, subkutanes Fettgewebe, Muskulatur, Haut, Haar

Figure A.5: Nutritional anamnesis applied with IG patients

A.2.5 Evaluation of interventions



Pat.-Code:																					
Interventionstag	1	2	3	4	5	**Interventionstag**	1	2	3	4	5	**Interventionstag**	1	2	3	4	5	**Interventionstag**	1	2	3	4	5
Aufenthaltstag						Aufenthaltstag						Aufenthaltstag						Aufenthaltstag					
Temp. (erhöht)						**Mittag**						**Abendbrot**											
Gewicht																							
Bedarf (kcal, g_{Prot})																							
Ödem-info																							
Untersuchg. (Zeit)																							
nüchtern (Mahlzeit)																							
Fl. i.v. (ml)																							
Substrat																							
Supplemente (Ressource)																							
Compliance (1-5)																							
Vit-/MS-NEM																							
EN (Substrat)						gesamt	◯	◯	◯	◯	◯												
Volumen						***kcal/Prot.-Menge***																	
Komplikation						ZMZ																	
Anzahl Medikamente																							
Antibiotika i.v.																							
Antibiotika p.o.																							
Frühstück																							
						gesamt	◯	◯	◯	◯	◯												
gesamt	◯	◯	◯	◯	◯	***kcal/Prot.-Menge***																	
kcal/Prot.-Menge						ZMZ																	
ZMZ																							
						Energie (kcal/d)																	
						Protein (g/d)																	

Temp.=Temperatur, Fl. i.v.=Flüssigkeit intravenös; Vit./MS/NEM=Vitamine, Mineralstoffe, Nahrungsergänzungsmittel; EN=enterale Sondenernährung; p.o.=per os; ZMZ=Zwischenmahlzeit

REE=0.02219xweight+0.02118xheight+0.884xsex-0.01191xage+1.233 (0=female, 1=male)

Figure A.6: Nutritional intervention evaluation sheet, one sheet per patient

A.3 More data related to the ITT analysis

A.3.1 Caloric intake per meal and therapeutic approach

Table A.1: Caloric intake per meal and therapeutic approach

Variable	Randomisation	Mean (SD)	MD (min-max)	Variance	Significance
Breakfast	CG[1]	341 (151)	352 (0-676)	22758	0.475
	IG[2]	361 (112)	345 (138-754)	12604	
Morning snack	CG	40 (59)	13 (0-304)	3464	<0.001
	IG	114 (61)	105 (0-295)	3766	
Lunch	CG	279 (110)	278 (0-495)	12097	<0.001
	IG	363 (95)	366 (111-573)	8958	
Afternoon snack	CG	57 (68)	33 (0-250)	4590	<0.001
	IG	172 (70)	165 (0-394)	4947	
Supper	CG	343 (121)	346 (111-647)	14741	0.064
	IG	383 (112)	372 (151-640)	12606	
Bedtime snack	CG	32 (50)	8 (0-250)	2486	<0.001
	IG	133 (73)	118 (0-325)	5259	
Enteral nutrition	CG	1 (12)	0 (0-94)	133	0.549
	IG	17 (120)	0 (0-964)	14490	
Fortification	CG	2 (5)	0 (0-20)	27	<0.001
	IG	59 (40)	49 (0-202)	1639	
ONS[3]	CG	27 (112)	0 (0-750)	12509	<0.001
	IG	132 (121)	101 (0-546)	14616	
Intravenous supply	CG	22 (48)	0 (0-291)	2317	0.023
	IG	8 (32)	0 (0-225)	993	

[1] Control group
[2] Intervention group
[3] Oral Nutritional Supplements

A.3.2 Protein intake per meal and therapeutic approach

Table A.2: Protein intake per meal and therapeutic approach

Variable	Randomisation	Mean (SD)	MD (min-max)	Variance	Significance
Breakfast	CG[1]	9.7 (4.6)	9.6 (0.0-24.3)	21.5	0.498
	IG[2]	10.2 (3.7)	9.0 (3.4-17.1)	14.0	
Morning snack	CG	1.2 (2.9)	0.2 (0.0-19.8)	8.3	<0.001
	IG	4.2 (3.4)	3.1 (0.0-14.0)	11.5	
Lunch	CG	14.4 (6.6)	13.8 (0.0-31.5)	44.0	<0.001
	IG	19.6 (6.4)	20.0 (6.0-38.3)	41.1	
Afternoon snack	CG	1.9 (3.6)	0.5 (0.0-18.8)	13.1	<0.001
	IG	6.1 (3.0)	5.5 (0.0-14.0)	9.2	
Supper	CG	15.3 (5.3)	15.5 (4.4-27.6)	27.9	0.050
	IG	17.3 (5.9)	17.5 (5.7-30.6)	34.9	
Bedtime snack	CG	1.3 (2.8)	0.0 (0.0-18.8)	8.1	<0.001
	IG	7.4 (4.9)	6.5 (0.0-20.8)	23.6	
Enteral nutrition	CG	0.1 (0.5)	0.0 (0.0-3.8)	0.2	0.991
	IG	0.6 (4.7)	0.0 (0.0-038.6)	22.5	
Fortification	CG	0.3 (0.9)	0.0 (0.0-4.8)	0.7	<0.001
	IG	2.7 (2.1)	2.3 (0.0-9.8)	4.3	
ONS[3]	CG	1.9 (7.9)	0.0 (0.0-56.4)	63.2	<0.001
	IG	8.7 (7.5)	6.5 (0.0-25.6)	56.2	
Intravenous supply	CG	substrates did not contain any proteins			
	IG				

[1] Control Group
[2] Intervention Group
[3] Oral Nutritional Supplement

A.3.3 Protein intake according to food type/intervention

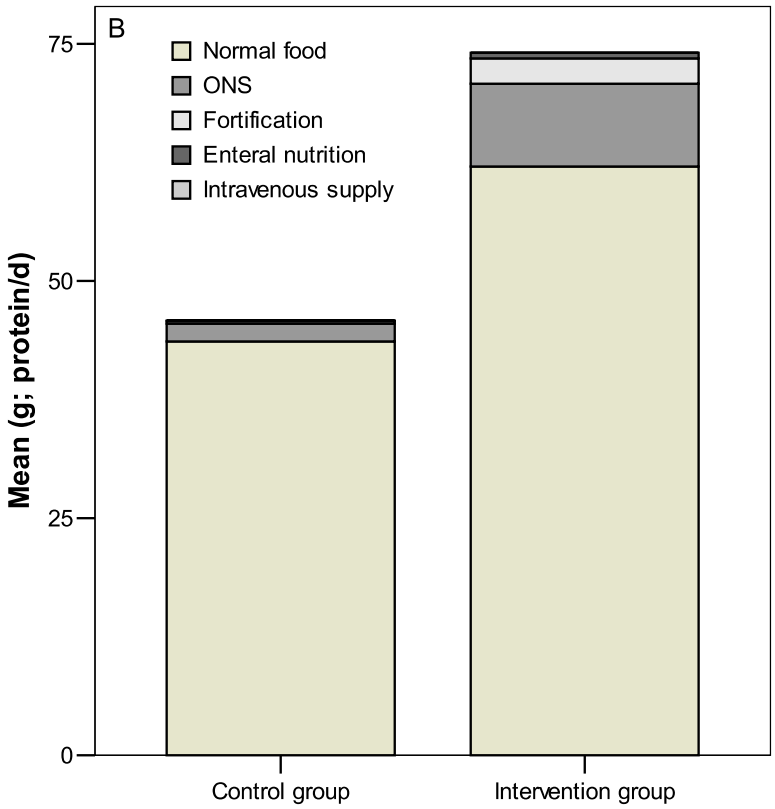


Figure A.7: Protein intake according to food type/intervention

A.3.4 SF-36 outcome data

Table A.3: SF-36 outcome data[b]

Scale[a]	Randomisation	Mean (SD)[c]	Median (min-max[c])	Variance	Significance
SF-36 PF	CG[1]	36 (26)	35 (0-85)	671	0.012
	IG[2]	51 (26)	50 (0-100)	699	
SF-36 RP	CG	19 (36)	0 (0-100)	1283	0.051
	IG	33 (42)	0 (0-100)	1761	
SF-36 BP	CG	67 (30)	72 (0-100)	898	0.845
	IG	66 (33)	74 (0-100)	1117	
SF-36 GH	CG	53 (17)	55 (10-92)	293	0.186
	IG	59 (22)	65 (15-97)	488	
SF-36 VT	CG	39 (17)	35 (5-85)	287	0.978
	IG	40 (24)	40 (0-90)	561	
SF-36 SF	CG	79 (23)	88 (25-100)	543	0.977
	IG	78 (26)	88(0-100)	661	
SF-36 RE	CG	67 (44)	100 (0-100)	1944	0.365
	IG	72 (44)	100 (0-100)	1951	
SF-36 MH	CG	70 (18)	72 (12-100)	331	0.784
	IG	71 (19)	72 (24-100)	366	
SF-36 PCS	CG	32 (9)	30 (19-56)	74	0.033
	IG	37 (11)	35 (15-65)	119	
SF-36 MCS	CG	51 (11)	53 (22-72)	115	0.640
	IG	50 (11)	52 (25-66)	112	

[a] SF-36 abbreviations: PF-Physical Function, GH-General Health, RP-Role Physical, BP-Bodily Pain, SF-Social function, RE-Role emotional, MH-Mental Health, VT-Vitality, PCS-Physical Component Summary, MCS-Mental Component Summary

[b] for all SF-36 sub- and summary scales: n=49 (control group; CG) and n=55 (intervention group; IG)

[c] in % of 100 %

A.4 SF-36 QoL ITT study data compared to a healthy reference population

Table A.4: SF-36 baseline data and reference values[b]

Scale[a]	Group[c]	Mean[c] (SD)	Group[d]	Signifi-[d] cance	Variance[d] lower bound	Variance[d] upper bound
SF-36 PF	CG	23 (24)	IG	0.789	-13.18	7.47
			NG	0.001	-68.06	-53.06
	IG	26 (24)	CG	0.789	-7.47	13.18
			NG	0.001	-65.13	-50.28
	NG	84 (24)	CG	0.001	53.06	68.06
			IG	0.001	50.2779	65.13
SF-36 RP	CG	4 (9)	IG	0.230	-12.62	2.3
			NG	0.001	-80.19	-73.79
	IG	9 (23)	CG	0.230	-2.3	12.62
			NG	0.001	-78.79	80.19
	NG	81 (35)	CG	0.001	73.79	80.19
			IG	0.001	64.73	78.93
SF-36 BP	CG	50 (34)	IG	0.262	-4.93	24.26
			NG	0.001	-37.80	-15.94
	IG	41 (33)	CG	0.262	-24.26	4.93
			NG	0.001	-46.63	-26.44
	NG	77 (28)	CG	0.001	15.94	37.80
			IG	0.001	26.44	46.63
SF-36 GH	CG	48 (20)	IG	0.89	-10.35	6.99
			NG	0.89	-24.76	-11.60
	IG	50 (19)	CG	0.89	-6.99	10.35
			NG	0.001	-22.45	-10.55
	NG	66 (21)	CG	0.001	11.60	24.76
			IG	0.001	10.55	22.45
SF-36 VT	CG	25 (18)	IG	0.524	-4.33	11.63
			NG	0.001	-42.68	-30.82
	IG	21 (18)	CG	0.524	-11.63	4.33
			NG	0.001	-46.01	-34.80
	NG	62 (19)	CG	0.001	30.82	42.68
			IG	0.001	34.80	46.01

continued

Table A.4: SF-36 baseline data and reference values *(cont.)*

Scale[a]	Group[c]	Mean[c] (SD)	Group[d]	Signifi-[d] cance	Variance[d] lower bound	Variance[d] upper bound
SF-36 SF	CG	67 (32)	IG	0.285	-4.90	22.36
			NG	0.001	-31.26	-10.74
	IG	58 (31)	CG	0.285	-22.36	4.90
			NG	0.001	-39.04	-20.42
	NG	88 (19)	CG	0.001	10.74	31.26
			IG	0.001	20.42	39.04
SF-36 RE	CG	52 (48)	IG	0.932	-17.94	24.28
			NG	0.001	-50.84	-19.89
	IG	49 (49)	CG	0.932	-24.28	17.94
			NG	0.001	-53.40	-2.68
	NG	88 (29)	CG	0.001	19.89	50.84
			IG	0.001	23.68	53.40
SF-36 MH	CG	63 (17)	IG	0.207	-2.30	14.05
			NG	0.001	-15.36	-4.48
	IG	57 (21)	CG	0.207	-14.05	2.30
			NG	0.001	-22.12	-9.45
	NG	73 (17)	CG	0.001	4.48	15.36
			IG	0.001	9.47	22.12
SF-36 PCS	CG	27 (7)	IG	0.797	-4.09	2.35
			NG	0.001	-24.65	-20.10
	IG	28 (8)	CG	0.797	-2.35	4.09
			NG	0.001	-23.93	-19.07
	NG	49 (11)	CG	0.001	20.10	24.65
			IG	0.001	19.07	23.93
SF-36 MCS	CG	47 (11)	IG	0.231	-1.53	8.47
			NG	0.029	-7.56	-0.33
	IG	44 (12)	CG	0.231	-8.47	1.53
			NG	0.001	-11.0	-3.82
	NG	51 (9)	CG	0.029	0.33	7.56
			IG	0.001	3.82	11.0

[a] SF-36 subscales: PF-Physical Function, GH-General Health, RP-Role Physical, BP-Bodily Pain, SF-Social function, RE-Role emotional, MH-Mental Health, VT-Vitality, PCS-Physical Component Summary, MCS-Mental Component Summary

[b] for all SF-36 sub- and summary scales: n=56 (Control Group; CG), n=63 (Intervention Group; IG) and n=2861 (Norm Population; NG)

[c] ANalysis Of VAriance, values in %

[d] post-hoc tests

A.5 Main study results per protocol analysis

A.5.1 Baseline data

Table A.5: Baseline data

Variable	Randomisation	Mean (SD)	Median (min-max)	Variance	Significance
Age	CG[1]	76 (10)	76 (43-94)	108	0.206
	IG[2]	71 (16)	75 (21-94)	262	
Heigth	CG	165 (10)	164 (147-192)	101	0.375
	IG	166 (8)	166 (148-190)	69	
Body weight Admission	CG	66.0 (16.2)	65.9 (29.6-99.0)	260.9	0.465
	IG	68.2 (16.6)	67.7 (39.7-119.0)	276.8	
Vit C serum concentration	CG	26.8 (20.2)	22.5 (1.0-92.7)	407.9	0.109
	IG	33.1 (21.9)	27.9 (1.6-96.0)	481.6	
Vit D serum concentration	CG	44.9 (25.8)	35.5 (13.2-128.9)	665.1	0.121
	IG	52.1 (24.3)	47.7 (14.6-134.9)	589.3	
Glutathion serum concentration	CG	3.73 (2.06)	3.58 (0.36-9.00)	4.25	0.499
	IG	4.08 (2.44)	4.04 (0.32-14.99)	5.97	
NRS-2002 disease score	CG	1.1 (0.3)	1.0 (0-2.0)	0.1	0.011
	IG	0.9 (0.5)	1.0 (0-2.0)	0.2	
NRS-2002 nutrition score	CG	1.7 (0.7)	2 (0-3)	0.5	0.244
	IG	1.8 (0.6)	2 (1-3)	0.4	
Number oral drugs	CG	7 (3)	7 (1-12)	7	0.476
	IG	7 (3)	6 (1-14)	9	
REE[3]	CG	1339 (205)	1295 (970-1785)	41958	0.554
	IG	1361 (188)	1331 (1068-1768)	35456	
Sum of SF[4] and PAL[5]	CG	1.3 (0.1)	1.3 (1.2-1.4)	0.0	0.250
	IG	1.3 (0.7)	1.3 (1.1-1.4)	0.0	

continued

Table A.5: Baseline data *(cont.)*

Variable	Randomisation	Mean (SD)	Median (min-max)	Variance	Significance
TEE[6]	CG	1717 (251)	1684 (1272-2321)	63091	0.800
	IG	1728 (230)	1714 (1348-2211)	52982	

[1] Control Group
[2] Intervention Group
[3] Resting Energy Expenditure
[4] Stress Factor
[5] Physical Activity Level
[6] Total Energy Expenditure

Table A.6: Diagnoses according to ICD-10[3] coding

ICD-10 code	Randomisation	Frequency
Infectious and parasitic diseases	CG[1]	9
	IG[2]	4
Neoplasms, diseases of the blood	CG	14
	IG	10
Endocrine and metabolic diseases, diseases of the digestive system	CG	9
	IG	9
Diseases of the nervous system, the eye and adnexa	CG	2
	IG	5
Diseases of the circulatory system	CG	14
	IG	15
Others	CG	11
	IG	16

[1] Control Group
[2] Intervention Group
[3] International Classification of Diseases (10^{th} edition)

Table A.7: SF-36 baseline data per protocol[b]

Scale[a]	Randomisation	Mean (SD)[c]	Median[c] (min-max)	Variance	Significance
SF-36 PF	CG[1]	23 (24)	15 (0-85)	577	0.642
	IG[2]	25 (24)	20 (0-95)	583	
SF-36 RP	CG	3 (9)	0 (0-25)	73	0.081
	IG	9 (24)	0 (0-100)	581	
SF-36 BP	CG	50 (34)	41 (0-100)	1159	0.225
	IG	42 (35)	32 (0-100)	1194	
SF-36 GH	CG	49 (20)	47 (15-95)	401	0.689
	IG	51 (19)	52 (10-100)	369	
SF-36 VT	CG	25 (19)	25 (0-75)	347	0.362
	IG	22 (19)	18 (0-90)	363	
SF-36 SF	CG	68 (32)	75 (0-100)	1030	0.105
	IG	58 (32)	63 (0-100)	1049	
SF-36 RE	CG	53 (48)	67 (0-100)	2279	0.759
	IG	51 (49)	50 (0-100)	2424	
SF-36 MH	CG	63 (17)	60 (28-100)	287	0.252
	IG	59 (20)	56 (16-100)	410	
SF-36 PCS	CG	27 (7)	26 (10-42)	49	0.626
	IG	27 (8)	28 (10-47)	67	
SF-36 MCS	CG	48 (11)	46 (25-69)	122	0.160
	IG	44 (12)	44 (24-66)	146	

[a] SF-36 abbreviations: PF-Physical Function, GH-General Health, RP-Role Physical, BP-Bodily Pain, SF-Social function, RE-Role emotional, MH-Mental Health, VT-Vitality, PCS-Physical Component Summary, MCS-Mental Component Summary

[b] for all SF-36 sub- and summary scales: n=54 (CG) and n=56 (IG)

[c] in %

[1] Control Group

[2] Intervention Group

A.5.2 Results of the intervention

Table A.8: Intervention results[b]

Variable	Randomisation	Mean (SD)	Median (min-max)	Variance	Significance[a]
Kcal/d	CG[1]	1127 (345)	1152 (485-2082)	118893	<0.001
	IG[2]	1593 (332)	1583 (920-2827)	110246	
Protein/d	CG	44.6 (15.5)	44.9 (16.4-103.8)	241.3	<0.001
	IG	67.5 (15.8)	67.6 (32.4-102.2)	250.9	

[a] Repeated measure ANalysis Of VAriance
[b] Intervention periods 5 and 10 days (with n=59 and n=34, respectively)
[1] Control Group
[2] Intervention Group

Table A.9: Caloric intake per meal and therapeutic approach

Variable	Randomisation	Mean (SD)	MD (min-max)	Variance	Significance
Breakfast	CG[1]	354 (145)	359 (99-676)	20939	0.782
	IG[2]	362 (114)	348 (138-754)	13001	
Morning snack	CG	39 (55)	13 (0-304)	2992	<0.001
	IG	119 (59)	106 (20-295)	3540	
Lunch	CG	283 (101)	278 (98-495)	10172	<0.001
	IG	368 (96)	377 (111-573)	9186	
Afternoon snack	CG	57 (64)	42 (0-250)	4075	<0.001
	IG	183 (64)	174 (52-394)	4090	
Supper	CG	341 (114)	348 (111-647)	12890	0.012
	IG	396 (111)	408 (151-640)	12287	
Bedtime snack	CG	33 (51)	9 (0-250)	2551	<0.001
	IG	139 (71)	157 (1-325)	5072	
Enteral nutrition	CG	2 (12)	0 (0-94)	149	0.547
	IG	19 (127)	0 (0-964)	16199	
Fortification	CG	2 (5)	0 (20)	24	<0.001
	IG	63 (40)	56 (1-202)	1607	
ONS[3]	CG	27 (117)	0 (0-750)	13606	<0.001
	IG	141 (121)	120 (0-546)	14729	
Intravenous supply	CG	18 (44)	0 (0-291)	1966	0.050
	IG	6 (17)	0 (0-106)	299	

[1] Control Group
[2] Intervention Group
[3] Oral Nutritional Supplements

Table A.10: Protein intake per meal and therapeutic approach

Variable	Randomisation	Mean (SD)	MD (min-max)	Variance	Significance
Breakfast	CG[1]	10.2 (4.4)	9.7 (2.1-24.3)	19.4	0.853
	IG[2]	10.3 (3.9)	9.2 (3.4-17.1)	15.2	
Morning snack	CG	1.2 (2.8)	0.3 (0.0-19.8)	7.9	<0.001
	IG	4.4 (3.4)	3.2 (0.1-14.0)	11.9	
Lunch	CG	14.8 (6.1)	13.9 (4.1-31.5)	37.6	<0.001
	IG	19.8 (6.5)	20.0 (6.0-38.3)	42.1	
Afternoon snack	CG	1.7 (3.3)	0.7 (0.0-18.8)	11.1	<0.001
	IG	6.5 (2.9)	5.7 (1.4-14.0)	8.3	
Supper	CG	15.2 (4.8)	15.6 (4.4-27.6)	23.1	0.006
	IG	18.0 (5.8)	18.4 (5.7-30.6)	33.8	
Bedtime snack	CG	1.4 (2.9)	0.1 (0.-18.8)	8.4	<0.001
	IG	7.7 (4.9)	7.1 (0.0-20.8)	24.2	
Enteral nutrition	CG	0.1 (0.5)	0 (0-3.8)	0.2	0.547
	IG	0.8 (5.1)	0 (0-38.6)	25.9	
Fortification	CG	0.3 (0.9)	0.0 (0.0-4.8)	0.8	<0.001
	IG	2.8 (2.1)	2.4 (0.1-9.8)	4.5	
ONS[3]	CG	1.9 (8.3)	0.0 (0.0-56.4)	68.4	<0.001
	IG	9.4 (7.6)	6.6 (0.0-25.6	57.3	
Intravenous supply	CG	substrates did not contain any proteins			
	IG				

[1] Control Group
[2] Intervention Group
[3] Oral Nutritional Supplements

A.5.3 Outcome data

Table A.11: Further outcome data

Variable	Randomisation	Mean (SD)	MD (min-max)	Variance	Significance
LOS_e	CG[1]	14.3 (9.6)	13 (4-62)	92	0.432
	IG[2]	13.1 (6.4)	11 (5-38)	41	
LOS_f	CG	15.4 (10.1)	13 (4-62)	102	0.954
	IG	15.3 (8.8)	13 (5-41)	77	
LOS_g	CG	16.1 (10.2)	13 (6-63)	104	0.393
	IG	14.7 (6.9)	13 (6-38)	48	
LOS_h	CG	17.2 (10.6)	14 (6-63)	112	0.874
	IG	16.9 (9.0)	15 (6-42)	81	
LOS_i	CG	20.1 (17.5)	15 (7-120)	305	0.492
	IG	18.3 (10.2)	16 (6-48)	104	
Body weight discharge	CG	64.4 (15.8)	62.2 (29.6-99.9)	251	0.185
	IG	68.3 (15.5)	66.2 (41.6-109.9)	240	
Difference body weight	CG	-1.5 (3.0)	-1.4 (-9.1-4.8)	8.8	0.003
	IG	0.1 (2.8)	0.0 (-6.5-7.4)	7.6	
BMI[3]	CG	23.6 (4.9)	23.6 (13.2-42.7)	24.5	0.249
	IG	24.7 (4.8)	24.8 (16.3-36.7)	23.3	

[e] Study inclusion to possible discharge
[f] Study inclusion to definite discharge
[g] Ward admission to possible discharge
[h] Ward admission to definite discharge
[i] Hospital admission to discharge
[1] Control Group
[2] Intervention Group
[3] Body Mass Index

Table A.12: SF-36 outcome data[b]

Scale[a]	Randomisation	Mean (SD)[c]	Median (min-max)[c]	Variance	Significance
SF-36 PF	CG[1]	38 (27)	35 (090)	745	0.016
	IG[2]	51 (26)	53 (0-100)	686	
SF-36 RP	CG	19 (36)	0 (0-100)	1283	0.075
	IG	33 (41)	0 (0-100)	1693	
SF-36 BP	CG	69 (29)	73 (0-100)	858	0.598
	IG	65 (33)	73 (0-100)	1102	
SF-36 GH	CG	54 (17)	56 (10-92)	303	0.123
	IG	59 (22)	67 (15-97)	481	
SF-36 VT	CG	40 (18)	35 (5-85)	307	0.821
	IG	41 (23)	40 (0-90)	550	
SF-36 SF	CG	80 (23)	88 (25-100)	524	0.736
	IG	79 (25)	88 (0-100)	647	
SF-36 RE	CG	67 (44)	100 (0-100)	1944	0.458
	IG	73 (43)	100 (0-100)	1889	
SF-36 MH	CG	71 (19)	76 (12-100)	350	0.894
	IG	71 (19)	72 (24-100)	359	
SF-36 PCS	CG	33 (9)	30 (19-56)	74	0.037
	IG	37 (11)	35 (15-65)	117	
SF-36 MCS	CG	52 (11)	53 (22-72)	118	0.597
	IG	51 (11)	52 (25-66)	111	

[a] SF-36 abbreviations: PF-Physical Function, GH-General Health, RP-Role Physical, BP-Bodily Pain, SF-Social function, RE-Role emotional, MH-Mental Health, VT-Vitality, PCS-Physical Component Summary, MCS-Mental Component Summary

[b] for all SF-36 sub- and summary scales: n=50 (CG) and n=58 (IG)

[c] in %

[1] Control Group

[2] Intervention Group

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Closing remarks

A preface opens this thesis. Thus closing remarks will complete it but is there anymore to say? Every detail of the study was explained; the results were reported and discussed. And still, it feels incompleted without some rather subjective thoughts on the topic.

This study provided promising results related to nutritional support in hospitalised patients. Indeed, the results exceeded my expectations. Still, put in the context of Evidenced Based Medicine (EBM) they are of rather low quality due to soft outcome measures and a low number of patients. This is, however, a common challenge of nutrition trials (see discussion). The question is whether hard outcome multicentre nutrition trials can be performed successfully at all? One of the most famous scientists, *Albert Einstein*, stated what well fits to the problem of nutrition and food:

> Not everything that can be counted counts and not everything that counts can be counted.

Like in other studies investigating "services", the efficiency of intervention is related to the person doing the intervention, the heterogenity of the setting and the complexity of the intervention - much more than in a pharmaceutical trial that applies a pill. EBM is necessary to describe a drug and its effectiveness and safeness exactly. Of course, if normal food is supposed to be a treatment, then it underlies EBM as well. On the other hand, do we need evidence to emphasize on the importance of eating? And conversely, should one disregard food and eating during disease merely because an increase of survival rate has not been shown so far? Probably, the way how health care is provided influences the nutritional status of patients more than the missing evidence. Then, the phenomenon called disease-related malnutrition appears at least partly due to a lack of quality of care. If a hospital or ward works well, provides high quality care, has sufficient nurse-patients quotients etc., then malnutrition may occur less often. Malnutrition prevalence/incidence would then become an indicator for general quality of disease treatment and patient care. The relation of readmission rates and the quality of in-hospital care has been addressed [320]. A good nutritional management then probably leads to fewer readmissions (and not simply less cases) or fewer complications (and not simply patients with lower case-mix-index). However, a better quality of care can hardly be achieved as long as LOS is the outcome parameter of first choice. Then, discharging patients at all costs determines health care procedures, i.e. first of all diagnostics. So the treatments may be received in the ambulant setting where the revenues exceed the inpatient costs of the same treatment many times over.

Also, new and more invasive diagnostics and treatments influence the nutritional status beside the quality of care. They require special conditions which are unfavourable for

the nutritional status (see Introduction). Thus, if a comprised nutritional status is related to a bad outcome, than benefits related to the new disease treatment must be weight against its harms. If furthermore a treatment worsens the patient's QoL substantively, than - although a statistical difference in the outcome may have been reported (in concordance with EBM) - the patients should define what a benefit is to them. Additionally, patients should ask their doctors more often "How do you know?". It was the Swiss author and dramatist, Friedrich Dürrenmatt, who perfectly presented this challenge of science in the play "Die Physiker": if it is too difficult to handle a promising intervention safely, then hands away! New inventions in the health care system may not threaten world life in total but may be detrimental for the patients. In contrast, there may be few patients where the treatment helps perfectly. This issue is tackled by the recently upcoming "personalised medicine" [321]. The majority of patients may, however, profit from "personalised medicine" in the literal sense - a more human, patient-centred care. Then, less often is more [322]. Additionally, the costs of new inventions produce an increasing burden for the health care system and thus future generations. The former prime minister of Saxony, Prof. Kurt Biedenkopf, demanded once a reasonable and modest use of resources in order to fulfil the intergenerational contract [323]. Can we disregard the very basis of life (i.e. eating) while offering expensive treatments lengthening the "relapse free time" (and not even the lifespan) by a few months of a low quality of life? Is there anybody who wants this even if costs are refunded?

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Curriculum Vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version dieser Arbeit nicht veröffentlicht.