Disease-related malnutrition

Energy balance, body composition and functional capacity in patients on oral nutritional support after major upper gastrointestinal surgery.

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ABSTRACT

Background: Patients with cancer of the upper gastrointestinal tract are susceptible to malnutrition. Surgery is the only curative treatment although the procedure may negatively impact nutritional status. The aim of this thesis was to investigate energy balance, body composition and functional capacity during the first year but also long time after major upper gastrointestinal (MUGI) surgery in two groups of patient on oral nutritional therapy.

Methods: Oral nutritional therapy was given according to established practice guidelines at our hospital. Study A involved 15 individuals with a total gastrectomy performed at least 5 years ago. Study B involved 41 individuals during the first year after MUGI surgery. Several components of energy balance were measured, such as energy intake (4-day food record), resting energy expenditure (indirect calorimetry), physical activity (activity monitor ActiReg®, and activity interview $HPAQ_{modified}$) and total energy expenditure (TEE, doubly-labelled water DLW). Body composition and energy stores were measured with dual energy x-ray absorptiometry (DXA) from which total body skeletal muscle mass (TBSMM) could be calculated. Functional capacity was determined as maximal exercise capacity with a treadmill test.

Results: Study A: On group level nutritional therapy did not increase body weight, energy intake or TEE. Half of the patients increased their weight and half remained weight stable or lost weight. Presence of disease and BMI >25 affected weight development negatively. Both ActiReg® and $HPAQ_{modified}$ underestimated TEE at higher levels of activity compared to DLW. Actireg® estimated changes in TEE over time comparable to DLW.
Study B: Weight decreased particularly during the first month after MUGI surgery and was 7% lower after 12 months. Nearly 90% of the body mass loss was fat. One third of the patients remained weight stable and gained in fat free mass. In those who lost weight, 26% of the body energy content was lost 6 months after surgery corresponding to a mean negative energy balance of 340 kcal per day. Muscle mass and exercise capacity were related at all occasions and changes in muscle mass were related to changes in exercise capacity while energy balance did not directly influence the relationship. However, patients in negative energy balance, lost more muscle mass and reduced their exercise capacity compared with patients in energy balance. About one third of patients had low muscle mass before surgery.

Conclusions: The greatest weight loss following MUGI surgery occurred during the first month and persisted throughout the first year after surgery. The weight loss consisted primarily of fat and seemed to be persistent as weight loss in the same order of magnitude was found more than 5 years after surgery. Low muscle mass was common. Weight development varied, and approximately 30 (study B) to 50 % (study A) of patients increased in weight during the intervention. Co-morbidity and

BMI >25 seemed to be factors of importance. Muscle mass and changes in muscle mass affected exercise capacity. The importance of energy balance is unclear, but the results suggest that weight change affects muscle development and functional capacity.

SAMMANFATTNING

Bakgrund: Undernäring är vanligt hos patienter med cancer i övre mag-tarmkanalen. Kirurgi är den enda botande behandlingen även om ingreppet kan inverka negativt på nutritionsstatus. Syftet med detta avhandlingsarbete var att studera energibalans, kroppssammansättning och funktionsförmåga under det första året, men även lång tid efter stor övre gastrointestinal kirurgi i två grupper av patienter med oral nutritionsbehandling.

Metoder: Oral nutritionsbehandling bedrevs enligt etablerad praxis på vårt sjukhus. Studie A omfattade 15 individer som genomgått total gastrektomi för minst 5 år sedan. Studie B omfattade 41 individer under det första året efter kirurgi. De komponenter i energibalansen som studerades var energiintag (4-dagars matdagbok), energiomsättning i vila (indirekt kalorimetri), fysisk aktivitet (aktivitetsmätaren ActiReg® och aktivitetsintervjun $HPAQ_{modified}$) och den totala energiförbrukningen (TEE, dubbelmärkt vatten DLW). Kroppens sammansättning och energiförråd mättes med dual energy X-ray absorptiometry (DXA) varifrån skelettmuskulmassa beräknades. Funktionsförmåga mättes som maximal arbetskapacitet med ett test på gångmatta.

Resultat: Studie A: Oral nutritionsbehandling ökade inte kroppsvikt, energiintag eller TEE på gruppnivå men hälften av patienterna ökade sin vikt och hälften förblev vikt stabila eller förlorade vikt. Förekomst av sjukdom och BMI> 25 försämrade viktutveckling. Både ActiReg® och $HPAQ_{modified}$ underskattade TEE på högre aktivitetsnivåer jämfört med DLW. Actireg® beräknade förändringar i TEE över tiden jämförbart med DLW.
Studie B: Viktsförlusten skedde framför allt den första månaden efter kirurgi, och efter 12 månader hade kroppsvikten reducerats med 7%. Nästan 90% av viktsförlusten bestod av fett. En tredjedel av patienterna förblev viktstabila och ökade i både fettfrimassa och muskelmassa. Bland de som gått ner i vikt hade 26% av kroppens energiinnehåll förlorats 6 månader efter operation, motsvarande en negativ energibalans på 340 kcal per dag. Muskelmassa och arbetskapacitet var relaterade vid alla mätpunkter och förändringar i muskelmassa var också relaterade till förändringar i arbetskapacitet, medan energibalansen inte direkt påverkade förhållandet. Viktförlorande patienter i negativ energibalans förlorade dock mer muskelmassa och minskade sin arbetskapacitet jämfört med viktstabila patienter i energibalans. Ungefär en tredjedel av patienterna hade låg muskelmassa före operationen.

Slutsatser: Viktminskning efter stor övre gastrointestinal kirurgi inträffade främst under den första månaden och fortsatte under hela det första året. Viktminskningen bestod främst av fett, och verkar hålla i sig eftersom viktsförlust i samma

storleksordning förelåg ännu fem år efter operation. Låg muskelmassa var vanligt förekommande. Viktutvecklingen var heterogen, ungefär 30% (studie B) till 50% (studie A) av patienterna ökade i vikt under interventionen. Förekomst av annan samtidig sjukdom och ett högre kroppsmasseindex (BMI >25) var faktorer som påverkade viktutvecklingen negativt. Muskelmassa och förändringar i muskelmassa påverkade arbetskapacitet. Betydelsen av energibalans för detta samband är oklar, men resultaten tyder på att viktförändring påverkar muskelutveckling och funktionsförmåga.

LIST OF PAPERS

This thesis for the doctoral degree is based on the following papers referred to in the text by their Roman numerals:

I. Copland L, Liedman B, Rothenberg E, Bosaeus I. Effects of nutritional support long time after total gastrectomy. Clin Nutr 2007; 26:605-613.

II. Copland L, Liedman B, Rothenberg E, Ellegård L, Hustvedt BE, Bosaeus I. Validity of the Actireg® system and a physical activity interview in assessing total energy expenditure in long-term survivors after total gastrectomy. Clin Nutr 2008; 27:842-848.

III. Copland L, Rothenberg E, Ellegård L, Hyltander A, Bosaeus I. Body composition and energy balance in patients on nutritional therapy after major upper gastrointestinal surgery. (Manuscript)

IV. Copland L, Rothenberg E, Ellegård L, Hyltander A, Bosaeus I. Muscle mass and exercise capacity in patients after major upper gastrointestinal surgery. (Manuscript)

TABLE OF CONTENTS

ABBREVIATIONS

ASMM	Appendicular skeletal muscle mass
ASMMI	Appendicular skeletal muscle mass index
BF	Body fat
BFI	Body fat index
BMI	Body mass index
BW	Body weight
DLW	Doubly labelled water
DRM	Disease related malnutrition
DXA	Dual energy x-ray absorptiometry
EN	Enteral nutrition
ESPEN	The European Society for Clinical Nutrition and Metabolism
FFM	Fat-free mass
FFMI	Fat-free mass index
LOS	Length of stay
MET	Metabolic equivalents
MUGI	Major upper gastrointestinal
NCP	Nutrition Care Process
ONS	Oral nutritional supplements
PAEE	Physical activity energy expenditure
PAL	Physical activity level
PAR	Physical activity ratio
PN	Parenteral nutrition
REE	Resting energy expenditure
SD	Standard deviation
TBSMM	Total body skeletal muscle mass
TBSMMI	Total body skeletal muscle mass index
TEE	Total energy expenditure
TEF	Thermic effect of food
TG	Total gastrectomy
WL	Weight losing group
WS	Weight stable group
4D FR	4-day food record

INTRODUCTION

The primary cause of malnutrition in developed countries is disease, hence the expression "disease-related malnutrition" (DRM) [1]. Effects of the disease itself and/or effects of treatment can led to anorexia, difficulties in eating and swallowing or in the digestion and absorption of food and hence, influence on patients' food intake. A negative energy and nutrient balance will eventually result in metabolic, compositional, functional and psychological alterations that constitute the state of malnutrition. From a clinical point of view it is important to detect malnutrition at an early stage in order to prevent functional impairment and negative effects on clinical outcome, and enable less time- and resource-consuming interventions to be used effectively. Thus, the use of screening methods is advocated [2].

Based on measurements of resting energy expenditure (REE), it was until recently believed that a primary cause of weight loss was increased energy expenditure. However, the true determinant of energy balance is the relation between energy intake and total energy expenditure (TEE). With the possibility to determine TEE using double labelled water (DLW) it was discovered that TEE is unchanged in many patient populations. Instead TEE may even be lower than normal due to a reduction in physical activity. Therefore, correction of a low nutritional intake may be one of the most effective methods to prevent and treat DRM.

This thesis focuses on oral nutritional therapy and its effects on body weight, body composition and energy balance after major upper gastrointestinal surgery mainly due to cancer.

Major upper gastrointestinal (MUGI) surgery is an advanced and complicated treatment. It leads to major anatomical changes in the gastrointestinal tract and approximately 85% of gastrectomized patients have been reported to suffer from eating-related symptoms [3].

Nutritional therapy is often used in this patient group to prevent or reduce the negative effects of disease and surgery on nutritional status. To minimize the burden of different eating-related symptoms and to optimize energy and nutrient intake from ordinary food and supplements individualised dietary counselling is practiced.

However, there is a lack of evidence for the provision of oral nutritional therapy in managing DRM. There is also a lack of detailed descriptions of dietary counselling and oral nutritional therapy, which further complicates the interpretation and comparisons between different studies or populations [4].

Disease related malnutrition

Malnutrition means bad or faulty nutrition. The term is used to denote deficiency, excess or imbalance of a wide range of nutrients in both the presence and the absence of disease. There are inconsistencies and also confusion about both the definition and criteria for diagnosis and classification. Although both under- and overnutrition are forms of malnutrition, the term is often used to refer only to undernutrition. This convention will be used in this thesis, so that the term "disease-related malnutrition" refers only to disease-related undernutrition.

In the 1970s the problem of malnutrition in hospitals was recognized [5] and also the fact that most patients did not have their nutritional status examined during their hospital stay [6]. The former head of our department, professor Björn Isaksson, identified already in the 1980´s malnutrition in hospitals and denoted this state of nutrition as hospital related malnutrition [7]. He identified factors of importance to prevent malnutrition, i.e. provision of a catering system tailored to patients needs, provision of good tasting energy and nutrient dense foods, routine assessment of nutritional status at admission, identification of responsibility for nutrition care and the importance of education to medical students, doctors and ward staff in nutrition [7,8]. He also published guidelines for nutrition assessment and nutritional therapy [9]. Since that time progression has been slow in identification and treatment of malnutrition in most health-care systems. Today nutrition societies call for much of the same actions to prevent DRM, as Isaksson identified already 30 years ago [10].

Definition of DRM

The lack of a standard definition of DRM gives rise to much confusion both concerning detection, prevalence and consequences of malnutrition and also the possibility to evaluate the effects of nutritional therapy.

Malnutrition has been defined as "*The imbalance between intake and requirement which results in altered metabolism, impaired function and loss of body mass*" [11]. Allison proposed a clinical definition of undernutrition as "*A state of energy, protein or other specific nutrient deficiency which produces a measurable change in body function, and is associated with a worse outcome from illness as well as being specifically reversible by nutritional support*". Already at the beginning he considered this definition incomplete because it failed to recognise; 1. Suboptimal nutrition i.e. diminished glycogen stores or an absence of semi-essential nutrients such as glutamine during critical illness or trauma 2. The effect of acute disease on nutritional risk as it threatens normal food intake for a prolonged period [12].
Elia has defined malnutrition as "*A state of nutrition in which a deficiency or excess (or imbalance) of energy, protein and other nutrients causes measurable adverse*

effects on tissue/body form (body shape, size and composition) and function, and clinical outcome" [13].

DRM develops through two parallel processes and the course is affected by the presence or absence of metabolic changes, collectively referred to as catabolism (figure 1). Systemic inflammation leads due to its catabolic action to loss of fat-free mass (FFM), primarily skeletal muscle mass. The magnitude of tissue loss is related both to the intensity of the inflammatory reaction and its duration in time and is considered crucial as it furnishes substrate to fuel and support the acute phase response in trauma/disease [14].

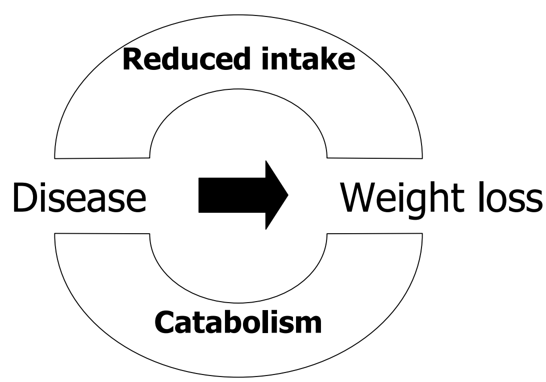

Figure 1. Disease-related malnutrition develops by two parallel processes and the course is affected by whether the disease causes an inflammation response or not.

Soeters et al [14] has recently proposed a definition that reflects this dual pathway pathophysiology of DRM and the possible contribution of diminished function from both abnormal body composition and inflammatory activity, "*Malnutrition is a subacute or chronic state of nutrition in which a combination of varying degrees of over- or undernutrition and inflammatory activity have led to a change in body composition and diminished function*".

Diagnosing DRM

Due to various conceptual definitions there is no consensus of the operationalisation of DRM i.e. "the development of a set of measurements that are a logic consequence of the definition of malnutrition and that should allow the assessment of nutritional state to be performed in a practical manner" [15] .
Recently, an aetiology-based construct suggestion for the diagnosis of adult malnutrition was published [16]. The nomenclature for nutrition diagnosis is proposed to distinguish between chronic starvation without inflammation ("starvation-related malnutrition"), chronic inflammation of mild to moderate degree ("chronic disease-related malnutrition"), and acute inflammation of severe degree ("acute disease or injury-related malnutrition"). However, operationalisation for this diagnostic approach is needed before it can be used in routine clinical practice.

The classification of malnutrition in the International Classification of Diseases (ICD) uses body weight expressed as standard deviation scores (z-scores) to diagnose malnutrition [17]. This approach is more suitable to children were the use of growth charts is a standard practice. The ICD does not include recent weight loss, recent intake, or inflammatory/disease-state which is all important factors in DRM. By adding cut-off's for BMI and unintentional weight loss in combination with a suboptimal intake, Australia have released a revised national version of the ICD-10 diagnosis of malnutrition adjusted with criteria for diagnosing DRM in adults [18]. Following criteria and cut-offs are used in the operationalisation of DRM and its severity;

- E43 Unspecified severe protein-energy malnutrition
    - BMI < 18.5 kg/m^2 or unintentional loss of weight (≥10%) with evidence of suboptimal intake resulting in severe loss of subcutaneous fat and/or severe muscle wasting
- E44.0 Moderate protein-energy malnutritition
    - BMI < 18.5 kg/m^2 or unintentional loss of weight (5-9%) with evidence of suboptimal intake resulting in moderate loss of subcutaneous fat and/or moderate muscle wasting.
- E44.1 Mild protein-energy malnutrition
    - BMI < 18.5 kg/m^2 or unintentional loss of weight (5-9%) with evidence of suboptimal intake resulting in mild loss of subcutaneous fat and/or mild muscle wasting.

The study of Meijers et al [15] among nutrition stakeholders concluded that a definition of DRM should include at least the elements *deficiency of energy, deficiency of protein and decrease in fat-free mass.* Also, *function* and *inflammation* are suggested to be important. Criteria for diagnosis of DRM were suggested to include at least the elements *involuntary weight loss, BMI* and *nutritional intake*. However, in this study there were disagreements on the level of importance of the elements and also regarding cut-off values.

Identification of DRM

In clinical practice, a variety of screening methods to detect DRM exists. A screening test refers to the detection of an otherwise unrecognised condition, which is usually amenable to treatment. Screening refers to a simple, rapid and general test that is undertaken by nursing, medical and other staff, often at first contact with patients, in order to identify those at risk of malnutrition. A recent review identified over 70 tests or tools for detection of malnutrition [19]. These tools vary significantly in their validity and reliability and also in applicability and usefulness [19]. However, since there is no universal agreement about the definition there is also a lack of reference methods to evaluate different screening tools. According to The European Society for Clinical Nutrition and Metabolism (ESPEN), the purpose of nutritional screening is to "*predict the probability of a better or worse outcome due to nutritional factors, and whether nutritional treatment is likely to influence this*". In 2003 ESPEN published a guideline for how undernutrition or risk for development of undernutrition can be detected [20]. Since screening method may vary according to circumstances, e.g. age or type of illness, they recommend different screening methods for the community, hospitals and in the elderly. Aware of the fact that no screening method has yet been validated with respect to clinical outcome, they state that these recommendations may need modification in the light of future experience.

In a recent review of the evidence for the impact of improving nutritional care it was found that nutritional screening alone is insufficient to achieve changes in outcome. Instead there is a need for suitable interventions to follow detection of patients with or at risk of malnutrition [21]. However, before initiation of nutritional therapy it is important to assess nutritional status and identify and label the nutritional problem with a nutrition diagnosis to be able to provide right treatment to right patient.

Prevalence of DRM

Reported prevalence varies according to use of different measures and methodology, cut-offs values, patient characteristics, medical diagnosis, and health-care settings [22]. There is also confusion about the prevalence since some studies report on the risk for malnutrition and not on malnutrition per se. Using body mas index (BMI) < 20 kg/m^2 as an indicator of risk for malnutrition, a mean estimated prevalence of underweight of approximately 18% (range 5%-37.5% has been reported in patients admitted to hospital with mixed diagnoses [1]. If unintentional weight loss is used, which has been identified as a better predictor of outcome than

BMI [23], an weight loss of >10% usual body weight is reported in up to 58% of general gastrointestinal surgical patients [1].

Based on 25 Swedish studies in health care settings (n = 5120) during 1980-1990's, the mean prevalence of protein and energy malnutrition was reported to be approximately 30% (range 5-87%). Four out of these 25 studies were performed on surgical patients (n = 558) and a prevalence of 40% (range 12-87%) were reported [24].

Unfortunately, development of malnutrition is not only a problem before hospital admission. Patients also develop malnutrition, or worsen an already existent malnutrition, during their hospital stay [22,25].

Consequences of DRM

Malnutrition has a diversity of effects, influencing every system of the body [1]. DRM is associated with impaired immune function, delayed wound healing and convalescence from illness and decreased functional status [26]. This affects the length of stay (LOS), outcome of medical care, survival and hence the costs to society [1,26]. DRM leading to prolonged LOS and increased complication rates also affect hospital costs. From studies that have investigated the impact of poor clinical outcome due to malnutrition, increased hospital costs of 26 to 77% have been reported [1].

Nutrition care process

The reasons why patients fail to meet their energy and nutrient needs are multi-factorial and include patient-specific factors, as well as factors related to the care system, such as provision of catering and clinical practice routines [21].

The guideline on nutrition screening from ESPEN [20] includes standards on screening at admission, assessment of undernourished patients, initiation of nutritional therapy, monitoring of outcome, communication of results and creating a patient care plan. A wide discrepancy between standards for nutritional routines and clinical practice in screening, assessment and initiating treatment has been identified in the Nordic countries [27]. Insufficient knowledge was pointed out by a great number to be the main barrier for good nutritional management [27].

Hospital and health care organizations should have a comprehensive hospital joint policy on how nutritional care should be designed [20]. This policy should include all steps in the nutrition care process (NCP);

Screening
↓
Assessment
↓
Treatment
↓
Monitoring and evaluation
↓
Communication

Each step in the process should be continuously documented, in the same way as any other part of the medical treatment. To ensure safe and effective nutritional care, the process needs to be standardized, established in the daily care routine and well known by all health care personal involved. A multi-professional approach is likely the most beneficial [10,21]. Since length of stay in acute care settings is limited and treatment of DRM is time-consuming, communication to other health care professionals when the patient is transferred is of great importance.

As indicated in the ESPEN guidelines on enteral nutrition, clinical processes can only be effectively implemented if there is a robust infrastructure [10]. Key elements mentioned for such a robust infrastructure on nutritional care are:

- Basic routines for nutritional care
- Identifying patients nutritional needs
- Providing individualised nutritional care when appropriate
- Making the most out of hospital food
- Choosing the right products
- Multi-professional working
- Communication and documentation
- Organisation and logistics
- Financial management
- Education
- Training

According to the American Dietetic Association (ADA) the NCP is intended to establish a standardized process for providing care [28]. This process is specific for the dietitian and involves four steps; nutrition assessment, nutrition diagnosis, nutrition intervention and nutrition monitoring and evaluation. A nutrition diagnosis identifies and labels a nutritional problem that the dietitian is responsible for treating independently [28]. It is distinct from the medical diagnosis. The importance of each step is highlighted since each step of the NCP is mandatory and informs the subsequent step. However, as new information is obtained the previous steps has to be revisited to reassess, add or revise nutrition diagnoses, modify interventions, or adjust goals and monitoring parameters [29]. For nutritional therapy to be successful, it is of equal importance to set the right nutrition diagnosis as the proper medical diagnosis is for adequate medical treatment.

Nutrition therapy in DRM

There is increasing evidence that insufficient food intake is of central importance in the development and progression of DRM [1]. Therefore, increasing energy and nutrient intake may be one of the most effective methods for prevention and treatment of DRM. Nutritional intake has also been identified as an important factor for outcome. Based on the one-day cross-sectional audit, NutritionDay in 2006, a progressive increase of 30-day mortality was associated with a reduced food intake [30].

In this thesis the focus is solely on nutritional therapy for prevention and treatment of DRM. Although the dual pathway pathophysiology of DRM – low intake and catabolism – may require multimodal strategies to combat, adequate nutritional intake is essential under all circumstances for an over all successful treatment of the patient.

Normal food should always be the first option when feeding the patients if not strong contra indication for oral intake exists [10,31]. By providing good quality food, appropriate in amount of energy and nutrients and consistency [32], and eating assistance when needed, many patients can meet their nutritional needs [33]. It is also important that meals are not missed and that restrictions on intake related to investigations or surgical procedures are minimized.

However, if the ordinary food served at the ward is not enough, nutritional therapy may be indicated. The overall aim of nutritional therapy is to try to ensure that total energy and nutrient intake meet the patients' needs (ordinary food + support) [33]. Strategies for nutritional support include oral nutritional supplements[1], food fortification[1], energy supplements[1], enteral tube feeding[1] and parenteral feeding (figure 2). Some clinical guidelines exist on a national level for treatment of DRM [24,33,35]. ESPEN provides disease-specific or treatment-specific guidelines for enteral and parenteral nutrition, as for example in surgery [36,37].

Dietary counselling, usually performed by a registered dietitian, is a supportive process, characterized by a collaborative counsellor-patient/client relationship, to set priorities, establish goals, and create individualized action plans that

[1] Ref 34. Commission directive 1999/21/EC: Dietary foods for special medical purposes.

acknowledge and foster responsibility for self-care to treat an existing condition and promote health-supportive process [28].

In a patient able to eat but in quantities insufficient to meet requirements, oral nutritional therapy is usually the first step in the provision of nutritional therapy. The aim is to increase energy and nutrient intake primarily from food. This has the potential advantages to offer a greater variety in taste and texture and the possibility to be tailored to individual preferences. Oral nutritional therapy can also be offered at a lower cost and requires less technical equipment and surveillance compared to artificial nutrition.

By individually tailored prescriptions oral nutritional therapy are adjusted to meet individual eating habits, preferences and physiological and energy/nutrients needs. Oral nutritional therapy can be divided into two sections (figure 2). *1) diet therapy* aims to optimize the intake of energy and nutrients from ordinary foods and adjust diet to better tolerate side effects of the disease or its treatment, e.g. consistency of diet [32], special diets [38], and energy and protein enriched diet [35]. When food, despite these adjustments, in not enough to cover energy and nutrient needs the use of *2) "dietary foods for special medical purposes"* [34] *and/or vitamin and mineral substitution* is initiated. Dietary foods for special medical purposes are "intended for the exclusive or partial feeding of patients with a limited, impaired or disturbed capacity to take, digest, absorb, metabolise or excrete ordinary foodstuffs or certain nutrients contained therein or metabolites, or with other medically-determined nutrient requirements, whose dietary management cannot be achieved only by modification of the normal diet, by other foods for particular nutritional uses, or by a combination of the two" [34]. "*Dietary foods for special medical purposes"* can either be consumed directly via oral intake (oral nutritional supplements and energy supplements), or as enteral nutrition ("feeding provided through the gastrointestinal tract via a tube, catheter, or stoma that delivers nutrients distal to the oral cavity"[39]) or added to food or drink as Food fortification [40].

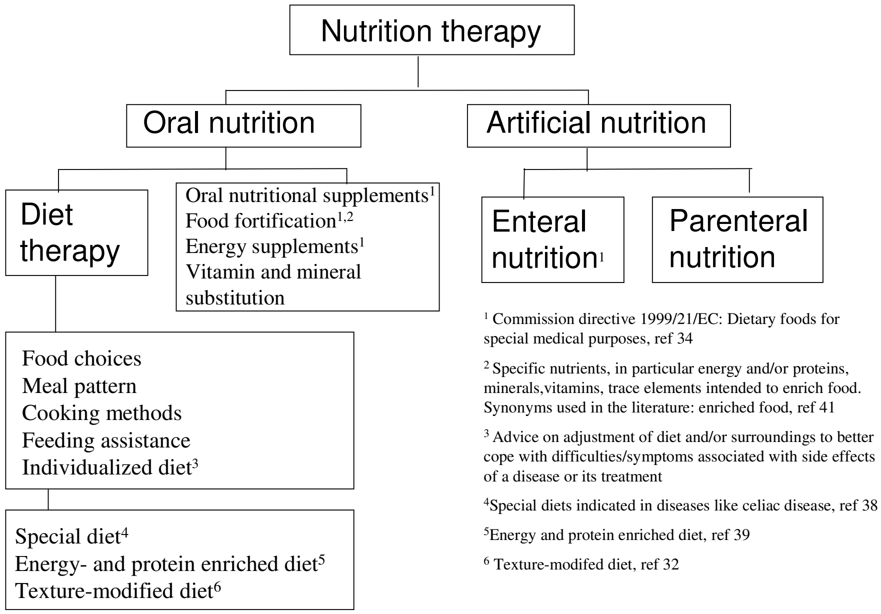

Figure 2. Structure of nutritional therapy.

The evidence base for the effects of nutritional therapy has been strengthened in recent years but this applies mainly to oral nutritional supplements (ONS), enteral nutrition (EN) and parenteral nutrition (PN) and not to dietary counselling or other measures carried out to increase intake of energy and nutrients from food [1,21,41]. Therefore much less is known about diet therapy and its curative and preventive effects in DRM. However, two recently prospective, randomized controlled trials in cancer patients on radiation therapy compared dietary counselling based on regular food, to both ONS and also to a control group. Dietary counselling led to a persistent increase (at 3 months) in energy and protein intake and this was opposite to ONS and the control group [42,43]. In these studies dietary counselling improved patients' nutritional status and QoL, thereby lessening radiation related morbidity. Another study randomized patients to receive either nutrition intervention based on a predetermined standard nutrition protocol (the Medical Nutrition Therapy, cancer/radiation oncology, protocol of the American Dietetic Association) or to standard care. Patients receiving nutrition intervention experienced less deterioration in weight, nutritional status and global quality of life compared to patients receiving standard care [44].

Also, meal fortification and additional snacks have been shown to increase energy intake in elderly institutionalized elderly [45-48]. In a study of malnourished patients admitted to medical or surgical wards who received two in-between meals and energy- and protein enriched meals, intake increased with 600 kcal and 12 g protein per day.

In many studies of DRM, nutritional therapy has been shown to improve nutritional status or clinical outcome. A combined meta-analysis of ONS and enteral tube feeding studies [1] across different patient groups and health-care settings showed significant reductions in mortality and complications rates. From this meta-analysis it was shown that reduction in length of hospital stay occurs in most trials. Improvements in body weight, although small, is seen especially in patient groups who are initially underweight (BMI <20). However, there is little evidence at present to suggest improvements in function or clinical outcome from fortification and counselling [41]. There is certainly a need of well-designed trials that investigates different strategies to improve dietary intake.

Body composition and energy metabolism

Body weight

Body weight measured on a scale is a practical and simple measure of the sum of total body components. Body weight adjusted for height [weight (kg)/height (m)^2] is a crude estimate of body energy stores, and is widely used to estimate nutritional state. Changes in body weight are determined by changes in body energy content (mainly fat and protein, and to a small extent glycogen), and changes in body water (and, to a minor extent minerals). Changes in energy content reflect the balance between energy intake and energy expenditure, and if hydration is assumed to be unchanged, body weight change is an estimate of energy balance. A weight loss >10% within the previous 3-6 months is considered as a clinically relevant weight loss [1] and is used in several screening instruments.

Body composition

The study of human body composition can be defined as "a branch of human biology which mainly focuses on the *in vivo* quantification of body components, the quantitative relationships between components, and component alterations related to various influencing factors" [49]. In this thesis, alterations in body composition related to disease and nutritional therapy have been explored.

The components of the human body can be organized into five separate body composition levels; a sum of all atoms, molecules, cells, all tissues/organs in the body or the whole body [49]. Body mass (weight) is the sum of the components at each of the five levels. Each level and its multiple components are distinct, but biochemical and physiological connections exist such that the five levels are consistent and function as an entity. There are relatively few direct measures of body composition. However, in a steady-state of body composition, relatively constant relationships are maintained between components at the same or different levels. This provides a matrix for creating explicit body composition equations, and development of multi-compartment methods for use when measuring the body composition indirect, and enables the estimation of body composition at different levels from one or more measurable properties of components.

Direct measures

The whole-body content of most frequently occurring atoms in the body can be measured in vivo as for example potassium by *whole-body counting*. At the molecular and cellular level total body water and the volume of extra cellular fluid can be measured by *isotope-dilution techniques* and bone mineral can be measured by *whole-body dual-photon absorptiometry* and *dual energy x-ray absorptiometry (DXA)*. No direct measure of cellular mass or extracellular solids exists. On the organ/tissue level most information comes from *cadaver studies or tissue biopsies*.

Imaging techniques, as *Computerized tomography* or *Magnetic Resonance Imaging,* are the main methods at this level. On the whole-body level, *anthropometric measures* such as body weight, body height, skin-folds, circumference and body volume can be measured directly.

Indirect measures

For indirect measure of body composition a large number of methods and models have been described. These methods vary widely in terms of availability and suitability for clinical use, as well as in precision and accuracy for determination of different body components and compartments. The choice of method in this study was based on availability and suitability for the groups studied, and a need for high precision to enable the study of relatively small changes in a limited sample. DXA's ability to measure small changes in body composition is supported by recent research findings [50].

Dual energy x-ray absorptiometry

DXA allows the body to be described as a 3-compartment model of mineral, mineral free soft tissue and fat. Measurements are made in the anteroposterior position and a series of transverse scans is made from head to toe at ~ 1 cm intervals (pixel) over the entire scan area. Whole body and regional measures of the three components can be made.

DXA uses a source that generates X-rays at two different energies, a detector and a computer system for imaging the scanned areas of interest. The principle of the method is that soft tissue and bone attenuate X-rays to different degrees. The body is divided into a series of pixels, and within each pixel the attenuation is measured and the ratio of the attenuations at these two energies is referred to as the R value. DXA assumes that the three different components are distinguishable by their X-ray attenuation properties. Soft tissue reduces X-rays to a much lesser extent than does bone mineral, and bone mineral are relatively easily distinguished form those with no bone present. Suitable calibration allows fat and lean fractions to be resolved from soft tissue pixels. The composition of these areas of soft tissue is extrapolated to the soft tissue overlying bone to produce total body fat and lean soft tissue. The algorithms to accomplish these extrapolations vary between manufacturers.

The advantages of DXA are that it is relatively quick; the whole body scan takes about 15 minutes or less. Radiation doses are low and DXA are used widely for subjects of all ages. Disadvantages are that the method assumes that hydration of fat-free tissue remains constant at 73% and severe over-hydration, such as ascites and oedema, may affect the resulting percentage of fat. Different manufacturers use different forms of calibration and different proprietary software solutions for the calculation of soft tissue composition in bone pixels, most often using the composition of soft tissue pixels adjacent to the bone pixel.

The precision of DXA are generally very good, with coefficients of variation of about 1% for bone mineral content, 2-3% for fat and 1% for lean soft tissue [50], but the accuracy is often considered due to the disadvantages described above, especially that values may vary slightly between manufacturers, devices and software versions.

Total body skeletal muscle mass

Based on the fact that a large proportion of total body skeletal muscle mass (TBSMM) is found in the appendages, and that the appendicular skeletal muscle mass (ASMM) is closely related to TBSMM, Kim et al [51] developed a TBSMM prediction model based on DXA measurements of arms and legs. The equation was validated against the reference method for total and regional muscle mass, magnetic resonance imaging. Later on the equation was refined considering inter- and intramuscular adipose tissue [52]. Although small in quantities (~1-2 kg), the presence of intramuscular adipose tissue within the skeletal muscle may bias the estimate of TBSMM.

Total energy expenditure

Total energy expenditure (TEE) is commonly divided in three components, resting energy expenditure (REE), physical activity energy expenditure (PAEE) and the thermic effect of food (TEF). REE, the energy required for basal, postabsorptive metabolism, is the largest component comprising 60-75% of TEE [53]. PAEE, the energy required to support physical movement, is the most variable component of TEE ranging from as little as 10% during bed rest or as much as 50% in elite athletes [53]. On average PAEE compromises 15-30% of TEE [53]. TEF represents the energy used to digest, metabolize and store ingested food and usually accounts for 10% of TEE [53].

DLW measures TEE in unrestrained humans in their normal surroundings over a time period of 1-4 weeks. It is regarded as the reference method for validation of other methods to assess physical activity and energy intake. DLW has an reported accuracy of 1-3% and a precision of 2-8% [54].

The principle of the method is that after a loading dose of water labelled with both stable isotopes of hydrogen (deuterium, ^{2}H) and oxygen (^{18}O), deuterium equilibrates throughout the body's water pool, and ^{18}O equilibrates in both the water and the bicarbonate pool. The bicarbonate pool in turn equilibrates to the flux of carbon dioxide, which, together with water, is the end product of energy metabolism and is eliminated through the lungs. Consequently, deuterium is eliminated as water, while ^{18}O is eliminated as both water and carbon dioxide. The elimination rates of deuterium and ^{18}O from the body are measured by mass spectrometric analysis of body fluid samples: blood, saliva or urine [55]. The difference between the two elimination rates is a measure of carbon dioxide production. This indirect measure of metabolic rate may then be converted to units of heat production by incorporating knowledge, or estimates, of the chemical composition of the foodstuffs being oxidized since this influences the energy equivalence of each litre of CO_2 produced.

The DLW method involves several assumptions about the behaviour of the isotopes, the body water pool and the exchange rates within that pool in the labelled subject [55]:

- The volume of the body water pool remains constant throughout the measurement period.
- The isotopes label only water and carbon dioxide in the body.
- The rates of water and carbon dioxide flux are constant during the measurement period.
- The isotopes leave the body only in the form of water and carbon dioxide.
- The concentrations of isotopes in the water and carbon dioxide leaving the body are the same as those in body water at that time (i.e. no fractionation).
- The background levels of the isotopes remain constant throughout the measurement period.

After the introduction of DLW in humans, it has been applied in studies to measure TEE in some disease states. Combining TEE with measures of REE permits the calculation of PAEE and this has broaden our understanding on the impact of disease on energy balance. Available studies suggest that TEE is unchanged or even reduced during different disease states. This is mainly explained by a reduction of PAEE. Thus, reduced energy intake rather than increased energy expenditure appears to be the likely mediator of the negative energy balance and ensuing weight loss seen in many disease states (Table 1).

Table 1. The doubly labelled water technique has offered the possibility to investigate the effects of disease on the components of energy metabolism in disease and hence, energy balance.

Reference	Population	REE	PAEE	TEE
Goran [56]	Burns (children) n=15	↑	↓	↔
Casper [57]	Anorexia Nervosa n=6 vs 6 contr	↓	↑	↔
MacAllan [58]	AIDS n=27	↑	↓	↔ ↓ BW-loss
Heijligenberg [59]	AIDS n=9 vs 9 contr	↑	↔	↔
Toth [60]	Heart failure n=26 vs 50 contr	↔	↓	↓
Toth [61]	Parkinson's disease n=16 vs 46 contr	↔	↓	↓
Poehlman [62]	Alzheimer's disease n=30 vs 103 contr	↓	↓	↓
Moses [63]	Advanced pancreatic cancer n=24	↑	↓	↓
Delikaniki-Skaribas [64]	Parkinson's disease n=10 weight losing vs n=10 weight stable	↔	↔	↔

Resting energy expenditure

REE is the largest component of energy expenditure, usually accounting for half to three-quarters of TEE. REE should be measured under standardized conditions i.e. in an awake, relaxed and overnight fasted state. The major part of whole-body REE (approximately 65%) stems from organs with high metabolic activity such as the liver, brain, heart and kidneys [53]. REE is closely related to body size, and thus standard values for energy expended or oxygen consumed can be given per unit of body weight.

REE is more variable in disease than in health and is influenced by the type, severity, phase of illness, nutritional status and a wide range of treatments [65]. Therefore, prediction of REE from standard reference tables or equations is more likely to be in error in disease than in health.

Thermic effect of food

TEF is mainly due to the energy cost of nutrient absorption and storage and increases significantly after a meal. The total TEF is approximately 10% of TEE but varies with the composition of the diet and is greater after consumption of carbohydrates and protein than after fat.

Physical activity energy expenditure

Physical activity can be defined as any bodily movement, produced by skeletal muscles, that results in increased energy expenditure [66]. Total amount of energy expenditure is determined by the amount of muscle mass producing bodily movements and the intensity, duration and frequency of the physical activity. The most important source of variation in energy expenditure between individuals is the muscular activity.

For a single activity the intensity can be expressed as metabolic equivalents (MET) or as physical activity ratio (PAR). A MET represents the ratio of energy expended at a particular activity divided by REE (measured or calculated) (1 metabolic equivalent=1 kcal kg-1 h-1 or 1MET=3,5ml O2 kg-1 min-1) and PAR is the total cost of an activity divided by basal metabolic rate. A compendium of energy costs of physical activities was published in 1993 [67] to facilitate the coding of physical activities and to promote comparability of coding across studies. In 2000 an updated version of the compendium was published and contains 605 specific activities [68]. The World Health Organization uses PAR in its physical activity index to express energy cost of activities (requirements per minute for various occupations) [69].

For a whole day the average intensity is expressed as physical activity level (PAL=TEE/REE) and can be described as light, moderate or heavy [69].

Different methods used to measure physical activity and energy expenditure include behavioural observations, diaries, physiological markers like heart rate, calorimetry (none of the former methods will be discussed in this thesis), recall questionnaires/interviews and motion sensors.

Dietary intake

Determination of dietary intake can either be done using prospective or retrospective methods. The choice of method depends on the purpose for which data will be used. Different dietary assessment methods give data on different output levels. Other factors of importance are resources in time, money, competence, population and population size. It is also important to interfere as little as possible with normal life but at the same time get as detailed descriptions as possible of food intake.

In <u>prospective methods</u> food intake is recorded at the time of eating, so called food records. Individuals note every food, snack or beverage consumed. Intake can either be weighed or estimated by households' measures or photographs/models. Shorter or longer periods of food intake can be recorded, usually over a period of 3-14 days [70]. To obtain representative data from an individual, the record must comprise several days and cover the true daily, weekly and seasonal variability in food intake. Another condition is that type and amount of food eaten are well described which requires a great accuracy of the person recording the food intake. Daily variation is the main factor determining the precision of recording methods and the extent of variation depends on the nutrient considered [71]. An average within-person day-to-day coefficient of variation for energy intake is reported to be 20-30% [72].

Retrospective methods rely on the memory of participant to recall food and diets eaten in the past. The methods used are recall of foods eaten, food frequency questionnaires, and diet history interviews.

Diet recalls are designed to quantitatively assess recent food intake in an individual by means of an interview. The most common is 24-hour recall although recalls from separate meals up to 7-days have been used [73].

Food frequency questionnaires were first developed for use in epidemiological investigations. They aim to estimate how often certain types of food are eaten. They can cover total intake or focus on specific groups of food or nutrients and also exclude or include information of portions sizes [74].

Diet history interviews require trained interviewers and are time-consuming. The method aims to capture habitual food intake during a specified period. The interview often starts with a 24 hour recall. To obtain an impression of how frequently particular foods is used and details of cooking methods the interviewer uses a questionnaire/checklist and for estimation of quantities photographic aids, food models or households measures is used [72].

In two reviews investigating validity of self-reported energy intake against DLW under-reporting was frequently observed [70,75]. The under-reporting was not confined to only one method but occurred across all dietary assessment methods [70,75]. It was originally believed that the phenomenon of under-reporting was linked to increased adiposity and body size but the most important mechanism for under-reporting in most age-groups appears to be “attitude to food”. This includes factors like body image, weight consciousness, social expectations and dietary restraint (a tendency to consciously control food intake in order to assist weight loss or prevent weight gain [75]). Gender, socioeconomic status and motivation also play a role in under-reporting.

There are very few criterion methods against which self-reported intake can be validated. Instead validation has involved comparison of one instrument against another. As such, it is the relative validity that is then examined. This type of validation will fail to detect true reporting bias if the two instruments have correlated errors. Instead, an external method with unrelated sources of error such as DLW is preferred for validation of recorded energy intake. The error of the

DLW technique is independent of self-reported intake error and true reporting bias can thus be detected [70].

Energy balance

As stated earlier changes in energy content of the body reflect the balance between energy intake and energy expenditure:

Energy intake - energy expenditure = change in body energy stores [76].

If energy intake equals energy expenditure there is no change in body stores and energy balance is achieved. However, if energy expenditure does not equal energy intake there is a simultaneous change in body stores and thus body weight. If hydration is assumed to be unchanged, body weight change is an estimate of energy balance.

However, change in body weight does not provide information on the composition of the lost body mass. The energy content of body mass depends on the ratio between fat-free mass and body fat since the energy density of body fat is approximately 10 times higher than that of fat-free mass [77].

The energy density of fat is well established at 39.4 MJ/kg, but the energy density of FFM, often taken as 3.7 MJ/kg [77] may be somewhat more variable due to variations in the proportions of protein and to a small extent glycogen in relation to water and mineral. Ideally, the energy containing components of FFM, i.e. protein and glycogen, should be quantified to obtain an exact measure of its energy content. This requires very complex methods *in vivo*, but due to the large differences in energy density between fat and fat-free mass mentioned above, variations will generate very small errors for total body energy content, except perhaps in very extreme situations of depletion.

We aimed to maximize utilization of the information obtained from DXA, and thus calculated the energy content of FFM on an individual basis as the sum of protein and glycogen, both with an energy density of 17 MJ/kg [69]. The sum of protein and glycogen was derived as FFM minus total body water (assumed constant at 73 % of FFM) and mineral (as the sum of bone mineral from DXA and soft tissue minerals, assumed constant at 1.29 % of total body water [78]. An independent measurement of total body water may have further improved the precision of this calculation, but was not available in the present study.

In most circumstances, except in total or pronounced starvation, energy balance is close to zero, or at least numerically much smaller than its components energy intake and expenditure. This also forms the basis for validation of energy intake measurements from total energy expenditure by DLW. Given the large measurement errors of especially energy intake measurements in humans under free-living conditions, energy balance cannot be reliably calculated from its components. The concept of using differences in body composition at two or more points in time offers a very precise way of determining long-term energy balance in free-living humans and groups of patients.

Upper gastrointestinal cancers

As for most malignancies, gastric, oesophagus and pancreatic cancers are mainly diseases of the older age groups, with more than 80% of new cases in Sweden being over 60 years of age at diagnosis [79].

Gastric cancer

Gastric cancer is the fourth most common cancer worldwide [80]. It is a disease with a high death rate making it the second most common cause of cancer death worldwide after lung cancer [81]. It is more common in men and in developing countries [80].

In Sweden, gastric cancer accounted for 1.7% in men and 1.3% in women of all new cancer cases in 2008 [79]. There is a remarkable decrease in upper digestive tract cancer incidence, which is mainly attributable to a reduction in gastric cancer, during the latest 20-year period (incidence rate 1989, 36.9/100 000 and incidence rate 2008 20.6/100 000). The decreasing trend has been constant since the start of the incident-registry in 1958. In 1960 gastric cancer was in second place of malignancies, and in 2008 it was no longer among the ten most common cancer forms in Sweden. This positive trend is assigned to changes in dietary habits, improvements in preservation and storage of food and a reduced prevalence of Helicobacter pylori [82].

Cancer is the second leading death cause in Sweden but mortality from gastric cancer has steadily declined over the period 1987-2007 for both men and women [83]. Survival from gastric cancer is fairly good only in Japan (52%) where mass screening has been practiced since the 1960s [80]. The prognosis of gastric cancer in Europe and the United States is still rather poor because of late diagnosis and advanced stage at diagnosis [80]. In Sweden the 5-year survival rate following diagnosis of gastric cancer is around 20%. After surgery and with the addition of radiation therapy and/or chemotherapy the 5-year survival rate is approximately 50% [82].

Gastric cancer is often asymptomatic or causes only nonspecific symptoms in its early stages. By the time symptoms occur, the cancer has often metastasized to other parts of the body, one of the main reasons for its poor prognosis. Frequent symptoms that affect food intake and induce weight loss are loss of appetite, nausea and abdominal pain. The only treatment for cure is surgery. Average preoperative losses of 3-11% of pre-illness body have been reported [84-91].

Oesophageal cancer

Oesophageal cancer is the eighth most common cancer world wide and the sixth most common cause of death from cancer [80]. Cancer of the oesophagus has a very poor prognosis with a 5-year survival of about 10 % of the cases in Sweden [82]. Oesophageal cancer is not common in Sweden, comprising only 0.8 % of all new cancer cases in 2008 [79]. It is more than twice as common in men [79]. Tobacco and alcohol are main contributors to its development in Europe and North America [80]. Recently, there appears to be an increase in western countries of adenocarcinomas of the oesophagus. The most likely explanation seems to be the increasing prevalence of Barrett's oesophagus as a consequence of gastro-oesophageal reflux, which is becoming more common with increasing levels of obesity [80].

The disease stage determines treatment options and surgery is the preferred treatment for resectable disease [92]. In Sweden only 25% of the patients suffering from oesophagus cancer are candidates for surgery and the reported 5 year survival after oesophagectomy is 31% [93]. One common identified nutritional problem in patients awaiting an oesophagoectomy is dysphagia.

Pancreatic cancer

Pancreatic cancer is the eight most common cause of death world wide from cancer [80]. 1.5% of all new cancer cases in Sweden 2008 were pancreatic cancer and the relative 5 year survival was 3.8% for men and 4.1% for women [82]. Little is known of the etiology of pancreatic cancer but there is a strong relationship to tobacco smoking and chronic pancreatitis increases the risk twenty-fold [82].

Symptoms of pancreatic cancer are diffuse and are often detected in a late stage of the disease. The only treatment for cure is surgery and about 15% of the patients are candidates for surgery. However, almost 90% of these patients relapse sooner or later [82], although 5-year survival rates up to 25% has been reported after surgical resection [94].

Major upper gastrointestinal surgery, nutritional status and outcome

In gastric cancer patients body weight losses of 4-15% during the first year after surgery have been reported [84,89,91,95-104]. Suggested causes include postoperative symptoms such as early satiety, postprandial fullness, dysphagia, and dumping syndrome leading to a diminished food intake. Malabsorption of fat caused by loss of digestive enzymes of the stomach, decreased stimulation of pancreatic and biliary secretions, increased intestinal motility and bacterial proliferation within the small bowel [105] adds up to a mean energy loss of a few hundreds kilocalories per day in gastrectomized patients [100,106,107]. The perioperative weight loss appears to be difficult to regain and leads to a prolonged or persistent weight reduction in many patients [86,88,91,95,99,100,102,104,108-111].

In the late 80s Windsor and Hill [112] showed weight loss to be a basic indicator of surgical risk provided that it is associated with clinically obvious impairment of organ function. Based on a clinical assessment of weight loss and functional status they found that patients with a weight loss >10% and abnormal function had a significantly higher incidence of major complications, septic complications, pneumonia and a longer hospital stay compared with patients with a weight loss <10% or >10% but with a normal function. They concluded that only patients with an impairment of important bodily functions in addition to significant weight losses should be considered for preoperative nutritional repletion.

The general indication for nutritional therapy in the surgical patient are the prevention and treatment of undernutrition, i.e. correction of undernutrition before surgery and the maintenance of nutritional status after surgery [36].

In the immediately postoperative state postoperative interruption of oral nutritional intake after MUGI surgery is frequently seen. The routine is believed to protect the anastomosis, prevent severe bloating and distension. However, this policy is not evidence-based and the risks or benefits of early initiation of food are unclear [36]. A questionnaire survey in 5 European countries revealed a marked heterogeneity in practice with particular reference to nutrition and oral intake and this is probably a reflection of the paucity of evidence [113]. Up to date, three studies have compared the routine ”nil-by mouth” the first days after MUGI surgery to “food-at-will” the first or second day after surgery [114-116]. No differences in morbidity were found but ”food-at-will” led to a faster onset of flatus/resumed bowel function, reduced length of stay, reduced wound infections and weight loss. ”Food-at-will” is suggested to promote faster postoperative recovery and a better quality of life for patients and through the activation of normal digestive reflexes it may elicit an important impact on gut recovery, which is central in overall recovery after MUGI surgery [36,115]. According to ESPEN Guidelines the amount of initial oral intake should be adapted to the state of gastrointestinal function and to individual tolerance and interruption of nutritional intake is pointed out to be unnecessary in most patients [36].

There are few studies investigating the effect of diet therapy (figure 2, page 20) on intake, weight development and outcome after MUGI surgery. The methodological descriptions of oral nutritional therapy often described as dietary advice/dietary counselling are scares and comparison between studies difficult to perform.

Nicklin et al performed an interesting study with the aim to define what kind of advice patients and their relatives would like to receive on dealing with the post-operative symptoms associated with oesophagectomy and gastrectomy [117]. An updated version of a previously designed booklet with information to patients following oesophagectomy was developed, based on a literature review, a patient/relative focus group and experience from health care professionals'.
The revised booklet includes sections about the operation (details of oesophagectomy and gastrectomy), eating and drinking (swallowing, appetite, meal times), possible problems (dumping, nausea, diarrhoea etc), lifestyle after surgery, healthy eating (food suggestions and recipes) and after recovery (resuming a normal diet). However, the usefulness of the booklet is not evaluated.

Bozzetti [118] investigated the effects of nutritional support on postoperative complications in a meta-analysis of 1410 subjects who underwent major abdominal surgery for gastrointestinal cancer. Age of the patient, type of surgery and serum albumin had a significant association with the onset of postoperative complications. The risk of complications increased continuously with an increase in weight loss above 10%. The benefit of nutritional support (total parenteral nutrition, enteral nutrition, immune-enhancing enteral nutrition) compared to standard intravenous fluids was evident in all strata of their patient population but, it was more evident for the high risk group (pancreatic tumour, >75 year of age, low albumin levels) and for patients with severe weight loss.

AIMS OF THE STUDY

The overall aim of this thesis was to study energy balance, body composition and functional capacity in patients on oral nutritional therapy after major upper gastrointestinal surgery.

The following specific aims were addressed:

Study A:

- To evaluate the effects of 12 months oral nutritional therapy long time after TG, on body weight, body composition and components of energy metabolism. Also, to evaluate the components of the oral nutritional therapy, -individual dietary advice and oral nutritional supplements. *(paper I)*

- To validate TEE measured by an activity monitor – the ActiReg® system, and a retrospective physical activity interview - "Hyrim Physical Activity Questionnaire" ($HPAQ_{modified}$) using DLW as reference method long time after TG due to gastric cancer. Also, to investigate the ability of the methods to detect differences in TEE between baseline and 12 months follow up. *(paper II)*

Study B:

- To evaluate changes in body weight, body composition and body energy content, measured by DXA, during the first postoperative year after MUGI surgery in patients receiving nutritional therapy.
  Also, to describe the oral nutritional therapy and evaluate energy and macronutrient intake in relation to energy balance. *(paper III)*

- To study changes in TBSMM and functional capacity before, six and twelve months after MUGI surgery. Also, to investigate the relation between 1) muscle mass and functional capacity (measured as exercise capacity), and 2) if changes in muscle mass are related to changes in functional capacity and 3) if this relation may be influenced by energy balance. *(paper IV)*

OVERALL DESIGN AND METHODS

This thesis is based of two studies in which the studies are presented in two papers each (table 2).

Table 2: Overview of design in the two different studies.

	Study A		**Study B**	
Paper	**I**	**II**	**III**	**IV**
Design	Prospective, non-randomized clinical trial		Secondary analysis of a randomized clinical trial	
Participants	15 patients (5 women, 10 men) who had underwent TG due to gastric carcinoma more than 5 years ago.		41 patients (14 women, 27 men) during the first postoperative year after MUGI surgery.	
Methods	BW and height, Body composition by DXA, Dietary Intake by 4D FR, REE by indirect calorimetry, TEE by DLW	BW and height, REE by indirect calorimetry, TEE by DLW, PAEE by Actireg and $HPAQ_{modified}$	BW and height, Body composition by DXA, Dietary Intake by 4D FR REE by indirect calorimetry	BW and height, Body composition by DXA, Exercise capacity by treadmill
Intervention	Oral Nutritional therapy	Oral Nutritional therapy	Nutritional therapy	Nutritional therapy
Statistical analysis	Descriptive statistics mean (SD), Students t-test for dependent samples, Wilcoxon signed rank test	Descriptive statistics mean (SD), 95% CI, One-sample Kolmogorov-Smirnov test, Students t-test for dependent samples, Bland-Altman plot, Linear regression	Descriptive statistics mean (SD), One-sample Kolmogorov-Smirnov test, Students t-test for dependent and independent samples, ANOVA for repeated measures, Pearson product moment correlation coefficient, Fishers exact or Chi-square test	Descriptive statistics mean (SD), One-sample Kolmogorov-Smirnov test, Students t-test for dependent and independent samples, One-way ANOVA for several group comparisons, ANOVA for repeated measures, Pearson product moment correlation coefficient, Scatter dot plots, Linear regression, Fishers exact or Chi-square tests

TG ; Total Gastrectomy, MUGI; Major Upper Gastrointestinal, BW;Body Weight, DXA;Dual energy X-ray Absorptiometry, 4D FR;4-Day Food Record, REE;Resting energy expenditure, TEE;Total Energy Expenditure, PAEE;Physical Activity Energy Expenditure, $HPAQ_{modified}$; Hyrim Physical Activity Questionnaire.

STUDY POPULATIONS

Study A.

Long-time survivors (more than five years) after TG for gastric carcinoma, performed at the Sahlgrenska University Hospital, were invited to participate. They had to live at home and for logistical reasons live in the city of Gothenburg. They had to be without signs of recurrent cancer, dementia, severe illness, drug abuse and no major surgery performed or planned. Also, they had to show at least a 5% weight loss at inclusion as compared to their preoperative weight. The original intention was to include 25 patients, but only 18 long-term survivors could be identified from hospital records, of which 15 patients agreed to participate. Main reasons for this low patient availability at a reasonably large centre may be a mean high age at diagnosis combined with the poor prognosis. The study was carried out from May 1999 until May 2002.

Study B.

This is a secondary analysis of a previously reported study of postoperative nutritional therapy carried out from October 1995 until February 2000 at the Department of Surgery at the Sahlgrenska University Hospital. During this period 126 consecutive patients were included in the study for resection of the oesophagus, stomach, or pancreas. Forty-six patients (36%) were excluded prior to randomization as a result of disseminated disease, thus 80 patients were included for follow-up and eligible for the present analysis [89]. The initial study was a randomized controlled trial to evaluate the effects of prolonged (3 months) postoperative nutritional therapy by enteral nutrition versus parenteral nutrition versus the effects of no artificial nutrition. Initial inclusion criteria were major resective surgical procedures in the upper gastrointestinal tract when curative resection for patients with malignant disease was deemed possible. Additional inclusion criteria in this analysis were available measurements of body composition by DXA preoperative and 12 months postoperative. All three study groups received individualised oral nutritional therapy during the first postoperative year, prescribed by a dietitian based on a standardized protocol. All patients were judged to be clinically free from recurrent disease. Postoperative changes in body weight, body composition and exercise capacity did not deviate between the 3 randomized study groups and there were no significant differences in total energy and protein intake between the groups over time. Survival, as well as mean hospital stay, did not differ significantly among the groups. Hence, we merged the groups into one for the present analysis.

METHODS

Body weight

Pre-illness and preoperative body weight was collected from hospital records or by asking the patients. Body weight and height were measured at baseline and thereafter at month 1, 3, 6, and 12. BMI was calculated according to body weight (kg) divided by height squared (m^2).

Patients with a postoperative body weight loss $\geq$5% at 12 months were classified as weight losers and those who had lost <5% or gained weight were classified as weight stable *(paper III, IV)*

Body composition

Body composition was assessed with dual energy X-ray absorptiometry, DXA. Whole body DXA scans yield a 3-compartment model of fat, lean soft tissue, and bone mineral content for the whole body and also for specific regions of the body (i.e. arms, legs, trunk, and head). For body composition, data are commonly transformed to a classical 2-compartment model of fat (BF) and fat-free mass (FFM), where FFM is the sum of lean soft tissue and bone mineral content. DXA can also, using the sum of lean soft tissue in arms and legs (appendicular lean soft tissue), accurately determine skeletal muscle mass.

Study A *(paper I)*
DXA was performed at baseline and at 12 months using a Hologic QDR-2000 scanner (Mediel AB, Gothenburg, Sweden). Whole body scans were obtained and analyzed using enhanced array whole body software version 5.73A.

Study B *(paper III, IV)*
DXA measurements were performed at baseline, 6 and 12 months postoperatively with a LUNAR DPX-L (Scanexport Medical, Helsingborg, Sweden) with software version 1.31 and with the extended analysis program for total body analysis (LUNAR Radiation, Madison, WI, USA). The LUNAR DPX-L scanner uses a constant potential X-ray source and a K-edge filter to achieve a congruent beam of stable dual-energy radiation. Whole body scans were performed at the scan speed suggested by the system for each subject. A quality assurance test was conducted on a daily basis, as recommended by the manufacturer. Precision errors on the scanner, as determined from double examinations in 10 healthy subjects, were 1.7% for body fat, 0.7 % for lean soft tissue and 1.9 % for bone mineral content.
Total variation in appendicular lean soft tissue was not evaluated on this LUNAR-machine, but based on duplicate DXA measurements in 30 subjects on a Lunar Prodigy in our laboratory a coefficient of variation of 2.7 % was found.

Body energy content

Study B *(paper III)*

Differences in whole body energy content during the 12 month study were calculated from the measurements of BF and FFM. DXA measures BF and FFM with high precision. The coefficient of variation in body energy content was 1.02% on duplicate DXA measurements in 30 subjects on a Lunar Prodigy in our laboratory.

The energy density of BF is well established (9.4 Mcal/kg, or 39.4 MJ/kg) [77]. Since the energy density of FFM may be more variable we calculated it on an individual basis as follows;

Body content of protein and glycogen = fat free mass- [total body water (73% of fat free mass) + soft tissue minerals (1.29% of total body water [78]) + bone mineral content].

Energy content of protein and glycogen was calculated as 4.1 Mcal/kg (17 MJ/kg) [69].

Skeletal muscle mass

Study B *(paper IV)*

Using DXA regional measurements, appendicular skeletal muscle mass (ASMM) was defined as the sum of lean soft tissue in arms and legs (ALST) according to Heymsfield [119]. Total body skeletal muscle mass (TBSMM) was then calculated according to Kim et al [Model 1: 1.19 x appendicular lean soft tissue (kg) - 1.65)] [52].

Energy metabolism

Total energy expenditure

Study A

TEE by DLW was measured over a period of 14 days. Patients came to the laboratory in the morning after voiding and a normal breakfast. Prior to dosing, a second voiding was collected for determination of background isotope enrichment. Patients were given a weighed mixture of DLW, corresponding to 0.05 g of deuterium oxide (^2H_2O) and 0.10 g of oxygen-18-water ($H_2{}^{18}O$) per kilogram BW. The dose was flushed down the throat with a glass of tap water. Exact time of dosing was recorded, and the subjects were equipped with 30 screw-capped glass vials to be filled 8 and 12 h after dosing, and with the second voiding from day 2, 3, 4, 5, 10, 13, 14, 15, respectively. Exact voiding time was registered, and the urine samples were stored in freezer before delivery to the laboratory. Urine samples were analysed in triplicates on a Finnigan MAT Delta Plus Isotope-Ratio Mass

Spectrometer (ThermoFinnigan, Uppsala, Sweden) with a variation (SD) of 0.40 delta per mill for deuterium and 0.16 for oxygen. TEE from DLW was calculated by the multipoint method, using linear regression from the difference between elimination constants of deuterium and oxygen-18, with the assumptions for fractionation as suggested by IAEA [120]. The energy equivalence of the CO_2 excreted was calculated from estimated food quotient from a 4D FR [121].

Resting energy expenditure

REE was measured at baseline and at 12 months in study A and at baseline, 1, 3, 6 and 12 months in study B. Measurements were performed in the morning after an overnight fast by open-air circuit indirect calorimetry (Deltatrac metabolic monitor, Datex, Helsinki, Finland). Patients rested supine for 20-30 minutes in a quiet room with a temperature of 20-22°C before the start of the measurements. REE was then measured for approximately 30 minutes by open-air circuit indirect calorimetri with a ventilated hood. Metabolic rate was calculated from the oxygen consumption and carbon dioxide production using the Weir equation [122] and expressed per 24 h. *(paper I, II, III).*

Physical activity energy expenditure

Study A *(paper II)*

In the late 90s, when study A was planned, available motion sensor methods to assess physical activity energy were few [123] and DLW was just recognized as the gold standard for the validation of field methods [124]. In cooperation with the University of Oslo, we had the opportunity to use and validate a new promising motion sensor, the ActiReg® [125]. Also the HPAQ was developed in Oslo and had been validated against ActiReg® [126]. At that time I thought it would be interesting to try the interview technique in a clinical situation and with the opportunity to validate it against DLW.

ActiReg®

The ActiReg® system (PreMed AS, Oslo) uses combined measures of body position and motion to calculate energy expenditure and express physical activity [125]. It consists of two components, an activity monitor (ActiReg®) and a dedicated software (Acticalc®) for processing and presenting data and calculating energy expenditure. The device has two body position sensors (tilt switches) and two motion sensors connected by cables to a battery-operated storage unit. Each pair of one tilt switch and one motion switch is secured in a plastic bracket. One bracket is attached to the chest (sternum) and the other is fastened on the front of the right thigh. The tilt switches go from on to off when they deviate more than 45° from the vertical position. The motion sensors operate according to the all or none principle; they register either motion or no motion. The state of the body position and motion sensors is checked every 1 s. The sensors discriminate between the body positions sitting, standing, bending forward and lying supine and between the four states of no motion, motion on either chest or thigh sensor, or both. This gives the possibility

of 16 different combinations, with ActiReg® codes from 0 to 15. After a recording period, the stored data are transferred to a personal computer. ActiCalc® converts the data into information about body motion, body position and position changes for each minute. Every minute is assigned the most frequent registered body position. The pattern of the sixty codes recorded provides information about the physical activity (PA) level. ActiCalc® uses the activity factor to calculate an activity factor (AF). AF is then used to categorize PA into three levels: very low PA, low PA and moderate to high PA.
The different levels of PA together with the body position is given a metabolic constant taken from WHO's published reference values [127]. The metabolic constants are then multiplied with calculated or measured REE. The second calculation step takes the number of position changes into account by using the algorithm given in figure 3.

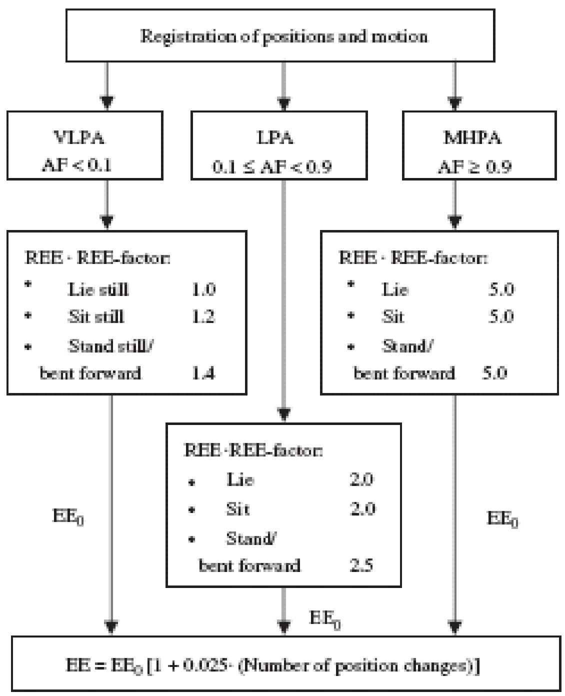

Figure 3. The calculation procedure for energy expenditure (EE) based on ActiReg®.

Patients were instructed to wear ActiReg® during 3 consecutive days within the 14-days DLW schedule, except during water activities (bathing/showering). They were carefully instructed on how to attach the sensors to their body. Measured REE was used for calculation of TEE.

The physical activity interview –HPAQ$_{modified}$

The physical activity interview was conducted using a modified version of Hyrim Physical Activity Questionnaire (HPAQ$_{modified}$) [128]. HPAQ has been developed to capture total energy expenditure including occupational time, transportation, recreation, leisure time and household activities. The modified version used in this study had no questions about work related time since the majority of patients (13/15) were retired. Instead the questionnaire focused more on low activity related activities, such as personal care, meal time and sleep. HPAQ is a retrospective interview covering the last 7 days and the interview takes about 20 minutes. It was performed at baseline and at 12 months, on the last day of the 14-days DLW schedule. The same interviewer conducted all interviews. Ainsworth's Compendium of Physical Activities [67] was used to calculate energy expenditure from the activities identified in the questionnaire and measured REE was used to calculate TEE. Intensity of sport-related activities were classified according to Borg's scale [129]. Time not reported was taken to be 1.5 METs corresponding to activities performed while sitting down and low intensity activities such as social or cultural leisure time activities. Calculations of TEE from the activity data were then performed in Excel®.

Dietary intake

Study A and B *(paper I, III)*

At baseline and at month 1, 3, 6 and 12, the patients completed a 4-day food record (4D FR). They were instructed to continue their normal eating habits and keep a complete and accurate record for 4 consecutive days, 3 weekdays and 1 weekend day (study B included 2 weekdays and 2 weekend days). Instructions were made to express all quantities in common household measures and to provide a complete description of the food items and also of the preparation and cooking. A detailed check-up was then made for incomplete recording, type of food and portion size with the aid of a portion-guide for estimating consumed amounts of food [130]. In study A check-ups were mostly performed in the patients own home except at baseline and 12 months were it was done at the out-patient clinic. In study B check-ups were always done at the out-patient clinic. The content of energy and nutrients were calculated using the software KOSTSVAR (Aivo, Stockholm, Sweden). The nutrient database used was the Swedish National Food Composition Tables [131].

On an individual level these data were used to design the individual oral nutritional therapy since it, besides energy and protein intake, described the type of food items used and the meal pattern.

Energy balance

Study B *(paper IV)*

Energy balance was defined as the difference in body energy content (see Body energy content page 39) at two different points in time, and expressed in kcal/day by dividing the absolute difference by the time interval between measurements.

Functional capacity

Study B *(paper IV)*

Functional capacity was evaluated by a treadmill test. The test started with the patient standing on the treadmill (Cardionics, Bandhagen, Sweden) for 1 min and thereafter walking at 1.5 km/h for 2 min without elevation. The test program then continued with walking at 1.5 km/h at 12% elevation for 1 min; thereafter, speed was increased by 0.1 km/h every 10th second until the patient chose to finish the test. The speed at which the patients finished the test was defined as maximal exercise power. The maximal mechanical power (W) at exercise was calculated by the software provided by the manufacturer (Medical Graphics Corp. St Paul, Minnesota, US) accounting for body weight, walking speed, and the elevation angle of the treadmill.

Oral Nutritional Therapy

Study A

Based on information from 4D FR and calculated energy and protein requirements all patients received individualized dietary counselling by a dietitian once a month in the patients' home and/or out-patient clinic or over the telephone. Energy intake was targeted to 40 kcal/kg body weight and day according to the Swedish hospital recommendation for weight gain [132]. Dietary advice were based on the energy and protein rich diet [132]. In this diet, preferential use of energy dense food items and the enrichment of food dishes by the addition of fat in the form of cream, sour cream, margarine or butter, oil and cheese is recommended to increase energy density (40-50% of total energy intake is from fat). Protein should contribute 18-20% of the total energy intake. The portion size is recommended to be half of a normal meal size at a given energy level and a compensatory higher meal frequency (6-8 meal/day) is recommended.

If energy and/or protein intake from food was considered insufficient and further diet modifications seemed difficult to implement, ONS were used depending on both estimated supplement needs and patient preference. Either energy- (150 kcal and 6 g protein/100 ml, Nutridrink®, Nutricia AB, Stockholm, Sweden) or a protein-rich supplement (100 kcal and 10 g protein/100 ml, Fortimel®, Nutricia, Stockholm, Sweden) was recommended depending on calculated requirements and reported intake from the 4D FR. The supplements were provided free of charge during the study. If the patients had problems with the intake of the first choice supplements, a clear juice-based liquid supplement (125 kcal and 4 g protein/100 ml, Ensini®, Nutricia, Stockholm, Sweden) and/or a supplement intended to use as a hot soup (100 kcal and 4 g protein/100 ml Ensure®, Abbot Nutrition, Stockholm, Sweden) and/or a energy powder supplement (380 kcal/100 g Maxijoule Super®, Nutricia, Stockholm, Sweden) were recommended depending on both estimated supplement needs and patient preference.

The dietitian checked compliance with the dietary advice and use of ONS monthly at the regular follow up. 4D FR, current weight, and questions about general health condition, with focus on post-absorptive symptoms, were used to monitor and re-assess oral nutritional therapy and nutritional status. After the study the delivered amount of ONS was compared with the consumed amount according to the 4D FR as an additional indicator of compliance.

Study B

Before and after discharge from the hospital, all patients received individualized dietary counselling by a dietitian. The dietary counselling was based on a standard protocol (table 3), but individualized based on reported intake of energy and nutrients, use of different food items and meal pattern from the 4D FR and patients' food preferences. If nutrition related surgical symptoms were present following advice were given; due to *early satiety,* low *appetite* and *food intake related pain* (odynophagia) a reduced portion size with a compensatory higher meal frequency was recommended. In order to prevent *epigastric fullness* and to optimize the energy and nutrient intake at the main meals, it was recommended to eat slowly and drink between meals. If at *risk of sub-/ileus* patients were advised to eat slowly and chew carefully and avoid foods with stringy fibres or risk of swallowing whole pieces (table 3). Energy enrichment of food dishes and use of energy dense food were recommended to prevent or treat unintentional *weight loss*. A high fat intake was recommended despite the possible presence of *fat malabsorption* and instead supplementation with pancreatic enzymes was used. *Dumping syndrome* was nutritionally treated with a diet low in single carbohydrates (hypoosmolar) diet [133]. The dietitian checked compliance with the dietary advice and use of ONS monthly at the regular follow up. 4D FR, current weight, and questions about general health condition, with focus on post-absorptive symptoms, were used to monitor and re-assess oral nutritional therapy and nutritional status

Energy intake was targeted to 35-40 kcal/kg body weight and day and protein intake was targeted to 1.5-2.0 g/kg body weight and day.

Table 3. Standard protocol for oral nutritional therapy.

Counselling	Diet	Dietary advice
Dietary counselling I *POD 4-6* *In hospital*	Liquid diet	Add between-meal snacks to the regular meals (a total of 5-6 meals a day) Use energy and protein rich ONS as first choice for between-meal snack Chew carefully and eat slowly Drink between meals not with meals
Dietary counselling II *POD 5-7* *In hospital*	Postoperative diet[a] ½ portion Prescription of ONS	Choice of energy dense food items and enrichment of food dishes with addition of fat as cream, butter, margarine, cheese, sour cream, and oil. If necessary adjust dose of pancreatic enzyme substitution Multivitamin tablet Individual dietary advice was adjusted to individual food habits and taste preferences
Dietary counselling III-VI *During the first3-4 weeks after discharge* *Telephone call once a week*	Postoperative diet[a]	Check of body weight, food and fluid intake, vitamin supplements and ONS. Dietary advice were repeated or adjusted as needed
Dietary counselling VII-XI *1,3,6 and 12 months after surgery* *Out-patient clinic* *If needed additional consultation from dietitian was offered.*	Postoperative diet[a]	Check of body weight, food and fluid intake, vitamin supplements and ONS (4-day food record). Dietary advice were repeated or adjusted as needed

[a]Principles of the Postoperative diet

Due to the risk for sub-/ileus, patients are recommended to avoid stringy meat and foods, rice, pasta, fruit peel etc. In hospital the postoperative diet is served as ½ portions due to the gastric restriction.

Avoid	Choose
Stringy meat	Minced meat, fish, sausages, eggs,
Rice, pasta	Potatoes/ mashed potatoes
Fresh vegetables	Cooked vegetables but avoid[b]
Fresh fruits	Cooked fruits but avoid[b]
Fresh baked bread, white soft bread	Bread older than one day, crisp bread, bread baked with coarse flour without whole kernels

[b] Stringy vegetables –asparagus, broccoli stalk, tomato peel, peas, corn, beans, lentils, mushrooms, stripes of onion, stringy fruit like pineapple and citrus, fruit peel, almond, nuts, dried coco flakes, dried fruit

POD, postoperative day; ONS, oral nutritional supplement.

Statistics

Descriptive values are presented as mean and standard deviation (SD). Data were tested for deviation from normal distribution by one-sample Kolmogorov-Smirnov test *(paper II, III, IV)*. For normally distributed variables, Students *t* test for dependent and independent samples was applied to analyse the difference between two groups or between two points in time *(paper I, II, III, IV)*. For skewed data, Wilcoxon signed ranks test were used in the analysis on food groups *(paper I)*.

Linear regression was used in the analysis of ActiReg® measurements to determine the association of different body positions and intensity of PA to the dependent variable PAL_{DLW}. Precision of the methods, estimated as the coefficient of variation (CV%) from the repeated measurements was calculated according to the formula $(\sqrt{\sum(x1-x2)^2/2n})/X*100$. The differences DLW - ActiReg® and DLW - $HPAQ_{modified}$ were examined against the reference method DLW in a modified Bland-Altman plot *(paper II)*.

Comparisons between more than two group means were analysed by one-way ANOVA. Statistical analyses of change in a variable over time (>2 measures) were tested with analysis of variance (ANOVA) for repeated measures, with Bonferroni correction for multiple comparisons *(paper III and IV)*.

To investigate relationship between variables Pearson product-moment correlation coefficient was used *(paper III and IV)*, together with scatter-dot plots and linear regression *(paper IV)*.

Nominal data were tested by Fishers's exact or Chi-square tests where appropriate *(paper III and IV)*.

A p value less than 0.05 was considered significant *(paper I, II, III, IV)*.

Calculations in paper I and II were made in SPSS for Windows version 11.5 and version 16.0 in paper III and IV (SPSS Inc., Chicago, Ill, USA).

RESULTS

Subjects

Study A

Of 18 patients identified from hospital records 15 were included. Two patients dropped of from the study due to illness in the family and problems to adhere to study protocol, respectively. Patient characteristics and time since surgery are given in table 4. Compared to pre-illness weight the group had lost a mean of 11% (n=13) at study start but one patient had actually resumed his pre-illness weight. Compared to preoperative weight, the group had lost a mean of 6 % but weight loss was less than 5% in 5 patients. One third of the patients had a BMI less than 22 and another third above 25.

Table 4. Subject characteristics at study start.

	Age study start	Years since TG	BMI preillness	BMI preop	BMI study start	Weight change from pre-illness to study start (%)	Weight change from preop to study start (%)
Women (n=5)	82	7	23.9	23.9	22.0	-8.0	-8.0
	65	8	29.6	29.6	27.5	-7.1	-6.8
	71	10	26.2	24.0	24.5	-6.5	1.9
	63	8	28.2	28.0	26.5	-5.8	-5.1
	68	12	23.2	20.2	18.4	-20.7	-8.9
Men (n=10)	74	7	25.7	22.6	21.5	-16.1	-4.9
	76	9	20.2	19.3	16.0	-20.7	-17.0
	79	9	27.8	25.9	24.5	-11.8	-5.3
	63	10	NA	26.3	20.5	NA	-22.1
	64	17	26.7	26.4	25.5	-4.8	-3.5
	55	9	22.5	21.1	19.2	-14.6	-9.0
	64	15	23.3	22.8	22.4	-4.1	-1.7
	61	11	24.7	21.7	25.2	2.0	16.2
	74	10	NA	24.1	25.1	NA	4.1
	64	9	30.5	29.3	24.6	-19.3	-15.9
Mean (n=15)	68 (7)	10 (2)	25.6 (3.0)	24.3 (3.2)	22.9 (3.2)	-10.6 (7.2)	-5.7 (9.2)

NA=not available, SD in paranthesis

Study B

In the initial study 80 patients were finally included and randomized. Of these, only 4% were lost due to missing DXA measurements. However, 31% of the patients were lost due to recurrent disease or death, and 14% were lost to follow up or withdrew their consent. The inclusion procedure and type of gastrointestinal resection is depicted in the flow chart in figure 4.

No differences were found between included and excluded patients in the preoperative variables. Preoperative patient characteristics is presented in table 5.

Table 5. Subject characteristics at study start. BMI and weight change before illness and preoperative to total gastrectomy (TG) (SD in paranthesis).

	Age study start	BMI preillness	BMI preop	Weight change Preop (%)	Weight change Preop (kg)
Women (n=14)	59 (11)	26.0 (2.6)	23.9 (1.7)	-7.7 (7.7)	5.5 (5.9)
Men (n=27)	60 (14)	25.7 (2.4)	23.5 (3.0)	-8.3 (8.5)	6.7 (7.0)
Mean (n=41)	60 (13)	25.8 (2.4)	23.6 (2.6)	-8.1 (8.2)	6.3 (6.6)

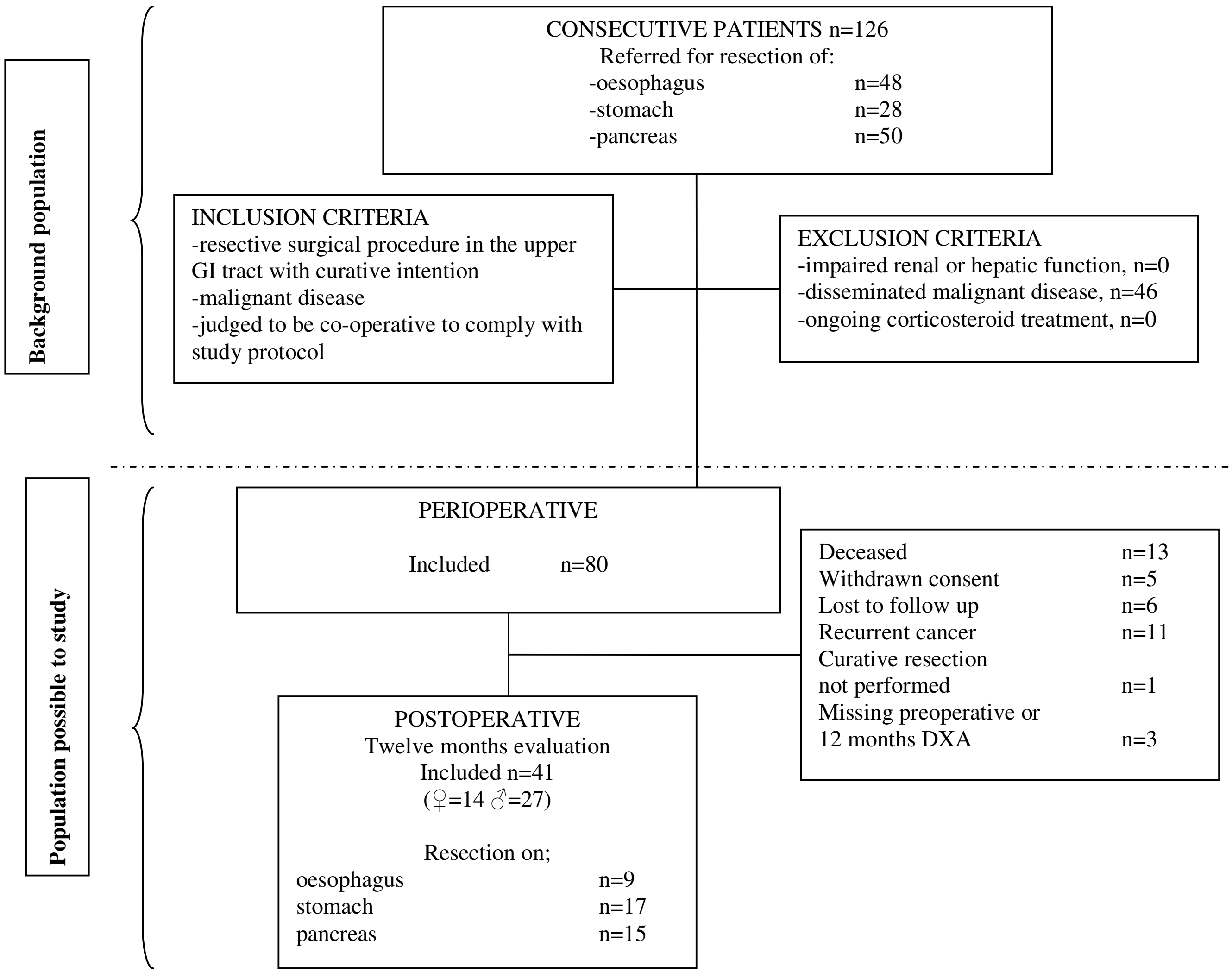

Figure 4: Flow chart describing the participants through each stage in study B.

Body weight

Study A

After the first month with dietary counselling there was a trend of weight gain. However, at 12 months no average changes in weight were found. However, weight development was heterogeneous, and six patients who had no signs of disease or health related problems gained weight whereas 5 patients who had various self-reported health problems lost weight, although not significantly. At inclusion 2 patients had a BMI >25 and although they at the beginning of the study claimed a wish to gain weight they later on expressed satisfaction with their current weight (table 6).

Table 6. BMI during the study year, total group and sub groups.

	n	Baseline	1 month	3 months	6 months	12 months
Total group	13	23.1 (3.2)	23.4 (3.2)**	23.3 (3.1)	23.1 (2.9)	22.9 (3.0)
Weight gaining	6	22.7 (2.2)	23.1 (2.3)	22.9 (2.0)	23.1 (1.9)	23.4 (2.1)*
Weight losing	5	22.6 (4.7)	22.9 (4.5)	23.0 (4.6)*	22.3 (4.2)	21.4 (4.0)
BMI>25	2	25.3 (0.2)	25.4 (0.6)	25.1 (0.5)	25.3 (0.1)	25.1 (0.2)

Standard deviation in parenthesis. * p< 0.05 **p=0.06-0.10

Study B

There was a significant reduction in average body weight during the first postoperative year, most of which occurred during the first postoperative month (3.9 (3.9) kg or 5.4%). This weight loss persisted throughout the first postoperative year, resulting in a total average body weight loss of 4.1 (6.9) kg or 6.9 (10.8)% (figure 2). There were no significant differences in body weight change between genders. There was a negative correlation between preoperative body weight loss and postoperative development of body weight. However, no relationship between preoperative BMI and postoperative development of body weight was found.

Although average body weight decreased during the study, 29% of the patients (men/women, 9/3) remained weight stable. More than 2 out of 3 (71 %) of the patients lost weight during the 12 months study (defined as a body weight loss of 5% or more -the weight losing group), and approximately 1 out of 3 (29 %) remained weight stable (-the weight stable group). Although the weight losing and weight stable groups did not differ in absolute body weight during the 12 months study, they did differ in development of body weight (figure 5). There were no significant gender differences between the weight losing and weight gaining groups. We found no preoperative differences between weight losing and weight stable patients in BMI, REE, energy intake/REE-ratio, reported energy intake/kg body weight, reported protein intake/kg body weight or length of artificial nutritional support. However, the weight stable group reported a higher preoperative weight loss (13.3 (9.4)% vs 6.0 (6.7)%, p<0.01).

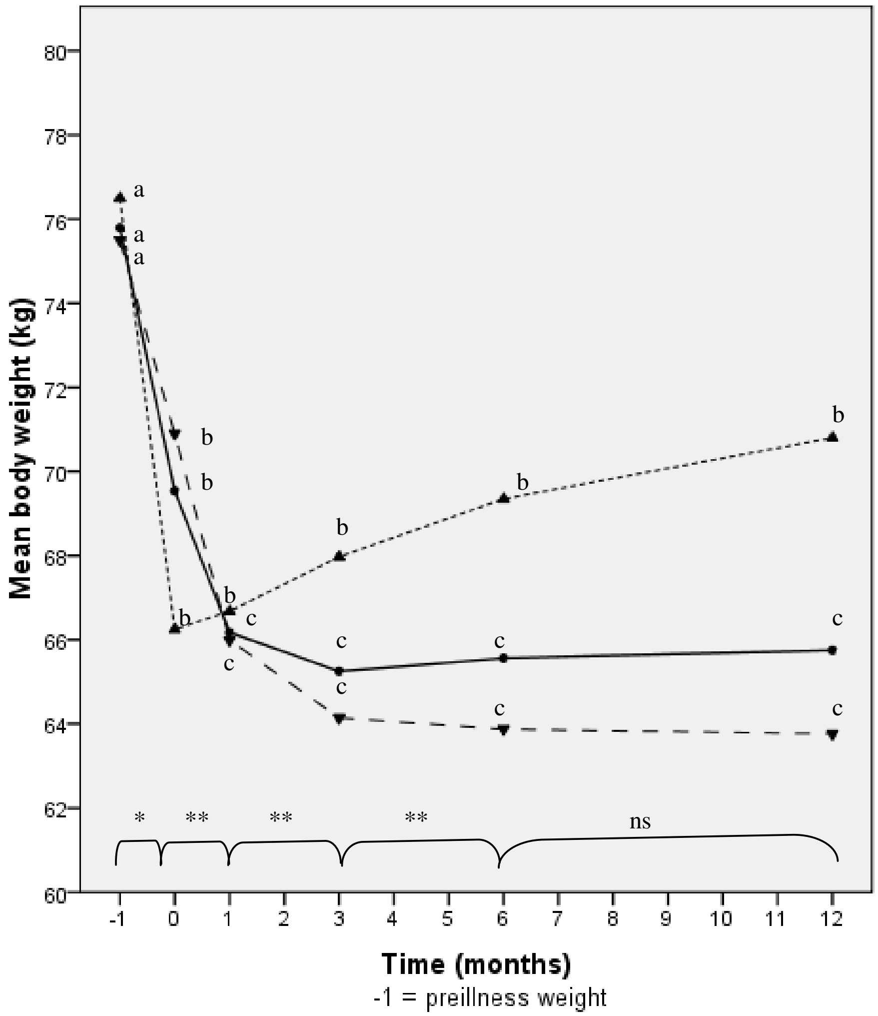

Figure 5. Development of body weight for the whole group (n=38) and for weight losing (WL, n=26) and weight stable (WS, n=12) groups during the first year after major upper gastrointestinal surgery. Different letters indicate significant difference between the various time points. Differences in development of body weight between the weight losing group and the weight stable group between different time points are indicated by *p< 0.05 and ** p<0.01, ns=not significant. ●Whole group, ▼WL, ▲WS

Body composition

Study A

Body composition showed no average significant changes in FFM or BF at 12 months. In the group of 6 patients who remained healthy during the study year there were a significant higher content of BF at 12 months while FFM were unchanged.

Study B

Compared to a Swedish reference material [134] both men and women had lower BMI, BFI and FFMI at all time points, though for women the difference in FFMI was not significant at 6 and 12 months postoperatively.

Most of the body mass lost was BF and at 12 months on average 26 % of preoperative BF stores were lost. No significant change in FFM was found and there were no significant differences between genders in body composition changes. (table 7)

Table 7. Body composition assessed by DXA (dual energy x-ray absorptiometry) preoperative (preop), six (6m) and twelve months (12m) after major upper gastrointestinal surgery. No significant differences in development of body weight, body fat and fat free mass were found between men and women.

	Women n=13	Men n=25	Total n=38
	mean (sd)	mean (sd)	mean (sd)
FFM_{preop} (kg)	40.3 (3.6) $^{\Delta\Delta\Delta}$	56.5 (5.8)	51.0 (9.3)
FFM_{6m} (kg)	40.4 (3.9) $^{\Delta\Delta\Delta}$	55.4 (4.8) $^{(*)}$	50.3 (8.5)
FFM_{12m} (kg)	40.5 (3.6) $^{\Delta\Delta\Delta}$	56.4 (5.5)	50.9 (9.1)
BF_{preop} (kg)	22.0 (4.4) $^{\Delta\Delta}$	16.8 (6.1)	18.6 (6.1)
BF_{6m} (kg)	17.1 (6.3) $^{*\ (\Delta)}$	13.1 (6.8) **	14.4 (6.8) ***
BF_{12m} (kg)	16.0 (7.1) $^{(*)\ (\Delta)}$	12.9 (6.3) **	13.9 (6.7) ***
$Fatness_{preop}$ (%)	35.2 (5.1) $^{\Delta\Delta\Delta}$	22.4 (5.7)	26.7 (8.2)
$Fatness_{6m}$ (%)	29.1 (7.3) $^{*\ \Delta\Delta\Delta}$	18.3 (7.3) **	22.0 (8.9) ***
$Fatness_{12m}$ (%)	27.3 (8.7) $^{*\ \Delta\Delta\Delta}$	17.9 (6.9) **	21.2 (8.7) ***

FFM, fat free mass; BF, body fat; SD, standard deviation. $^{(*)}$ p>0.05<0.10 vs preop, * p<0.05 vs preop, ** p<0.01vs preop, ***p<0.001 vs preop, $^{(\Delta)}$ p>0.05>0.10 vs men, $^{\Delta}$ p<0.05 vs men, $^{\Delta\Delta}$ p<0.01 vs men, $^{\Delta\Delta\Delta}$ p<0.001vs men

The weight stable group showed no significant change in BF but a gain in FFM between preoperative and twelve months measures. Among the weight-losing patients a major part of the weight loss was BF although loss of FFM was also significant.

Energy metabolism

Total energy expenditure

Study A

Total energy expenditure from DLW was 2430 (540) kcal/day at inclusion. This corresponds to 37 (4) kcal/kg/d, range 31-44 kcal/kg/d. After the 12 months intervention no change in average total energy expenditure was found.

Resting energy expenditure

Study A

The mean REE at inclusion (n=15) and the end of the study (n=13) were 1470 (260) and 1460 (250) kcal/day, corresponding to 22 (3) and 22 (3) kcal/kg/d, respectively. REE ranged between 17-29 kcal/kg/d and day at inclusion.

Study B

Mean REE preoperatively (n=41) and at the end of the study (n=39) were 1550 (190) kcal/day and 1550 (220) kcal/day, corresponding to 22 (2) and 24 (3) kcal/kg/d. REE ranged between 18-29 kcal/kg/d preoperatively, and 18-31 kcal/kg/d 1 year after surgery.

Physical activity energy expenditure

Study A *(paper II)*

The physical activity level measured by DLW and indirect calorimetry varied within a wide range, 1.30-2.12. Five patients had a PAL <1.50 and 6 patients >1.70.

TEE values by both ActiReg® and $HPAQ_{modified}$ were highly correlated to TEE values by DLW (r=0.89, p<0.001 and r=0.81, p<0.001). However, both methods underestimated (180 (254) kcal/day, p<0.05 and 130 (326) kcal/day, ns, respectively) although only significant for ActiReg®. Differences were more pronounced at higher levels of activity, and there was a systematic underestimation in individuals with $PAL_{DLW} \geq 1.65$ for both ActiReg® and $HPAQ_{modified}$ (figure 6). From the measurements with Actireg® it was found that the group with low PAL (<1.65) spent significantly more time in the supine positions compared to the group with high PAL (≥1.65).

In a multivariate analysis using the time spent in different body positions and activity levels as predictors only activity level=low remained a significant predictor for PAL.

Repeated measurements of TEE *(paper II)*

At 12 months TEE_{DLW} was unchanged, mean difference was 25 (166) kcal/day compared to baseline. Corresponding Actireg® measurements were -23 (118) kcal/day and $HPAQ_{modified}$ 153 (379) kcal/day and neither of them deviated from TEE_{DLW}. The 95% confidence interval of the difference between baseline and 12 months was -123 to 71 kcal/day from DLW, -62 to 108 kcal/day from ActiReg® and -382 to 76 kcal/day for $HPAQ_{modified}$.

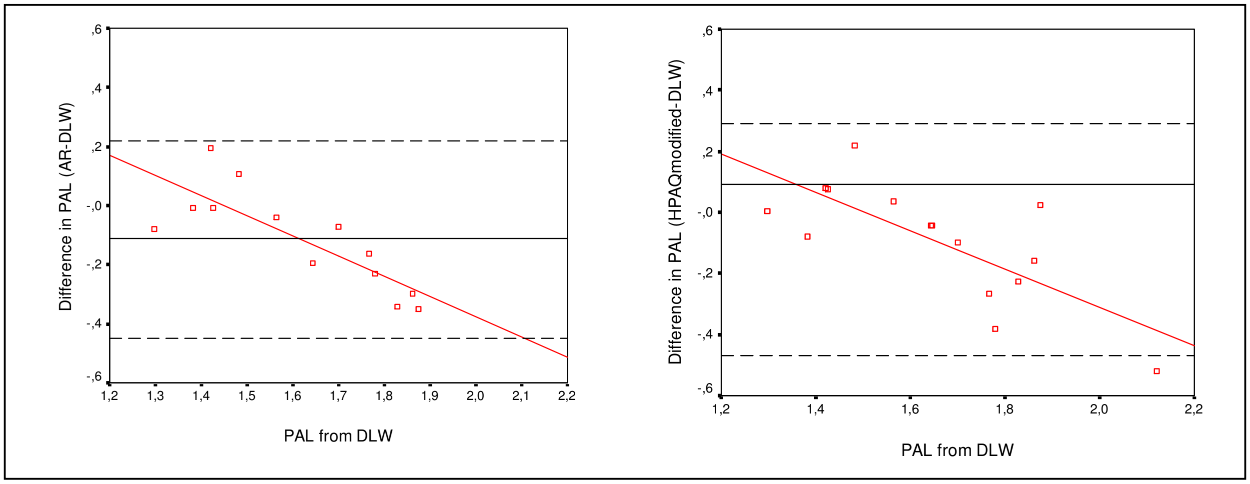

Figure 6. Differences between (a) PAL_{AR} and PAL_{DLW} are plotted against PAL_{DLW} and (b) $PAL_{HPAQmodified}$ and PAL_{DLW} are plotted against PAL_{DLW}. Limits of agreement of the mean difference (± 2 SD) are indicated by the dotted lines. For both comparisons the differences are more pronounced at higher levels of PAL_{DLW}, as illustrated by the negative slope of the regression line (r= -0.816, p<0.05 and r= -0.737, p<0.05 for (a) and (b) respectively.

Energy balance

Study B *(paper III and IV)*

During the first postoperative year, patients lost on average 44.2 (55.7) MCal (p<0.001) of their total body energy content, corresponding to 20 % of their total body energy content, with no significant difference between men and women. The group of weight losing patients lost 68.8 (38.6) MCal (p<0.001), corresponding to 29 %, whereas the small group of weight stable patients increased marginally their energy stores by 15.1 (13.1) MCal, although this was not significantly different from zero. However, the changes in body energy content between the two groups differed significantly (p<0.001) (table 7).

Expressed on a daily basis, the energy deficit during the first 6 months after surgery was 210 (260) kcal/day, whereas during the following 6 months energy balance was nearly achieved (-20 (150) kcal /day). Mean energy deficit during the entire 12 months was 120 (150) kcal/day. The weight-losing group lost on average an equivalent of 190 (110) kcal/day during the entire study and at 6 months this loss was 340 (170) kcal/day with no significant differences between men and women.

Table 8. Energy balance in the included patients and also in weight losing (WL) and weight stable (WS) groups, respectively. No significant differences in energy balance were found between men and women.

	Total n=38	WL n=26	WS n=12
(men/women)	(25/13)	(15/11)	(9/3)
Total Energy balance (mcal)	mean (sem)	mean (sem)	mean (sem)
Preop to six months postop	-39.2 (7.8)***	-61.9 (6.2)*** ΔΔΔ	10.0 (11.4)
Six months postop to 12 months postop	-4.4 (4.4)	-8.9 (5.4)	5.100 (7.5)
Preop to 12 months postop	-43.6 (9.3)***	-70.8 (7.7)*** ΔΔΔ	15.1 (13.1)

Repeated measures analysed with ANOVA and adjusted for pairwise comparisons by Bonferroni. * p<0.05 vs preop, ***p<0.001 vs preop. Differences between WL and WS analysed with unpaired Students t-test (Δ) p>0.05<0.10 vs WS, Δ p<0.05 vs WS, ΔΔΔ p<0.001vs WS. Sem; standard error of the mean.

Including energy balance as a predictor in a multivariate analysis between changes in total body skeletal muscle mass and changes in exercise capacity did not affect the slope of the line or increased the degree of explanation. However, the weight losing group who was in a negative energy balance had a significant higher proportion of patients who lost skeletal muscle mass compared to the weight stable group (i.e. in energy balance). This was also reflected in exercise capacity with a significant higher proportion of patients from the weight losing group showing a reduction in exercise capacity compared to patients in the weight stable group.

Calculated on the weight losing individuals the energy density of the lost body mass during the entire study was 8.3 (2.0) Mcal/kg body weight and the average body fat content of the weight loss was 87%. There were no significant differences between the energy density of lost body mass, and hence its' content of BF, between men and women

Dietary intake

Study A

At baseline all but 2 patients ate 6-8 meals per day as previously recommended. Several patients could not increase the total amount of food eaten due to symptoms commonly seen in TG patients like poor appetite, postprandial symptoms and early satiety. For many patients further diet modifications seemed difficult to implement, as they followed earlier diet recommendations. Mean energy density was 0.97 kcal/g. Supplemental ONS were prescribed to complement existing food intake in a majority of patients. However, mean meal frequency did not increase nor did the mean intake of energy- and protein, instead it seems like ONS replaced or suppressed ordinary food intake.

On a group level the 4D FR underestimated energy intake slightly but this was not significant. However, a Bland-Altman plot revealed a large spread in individual values of differences between energy intake and total energy expenditure (figure 7).

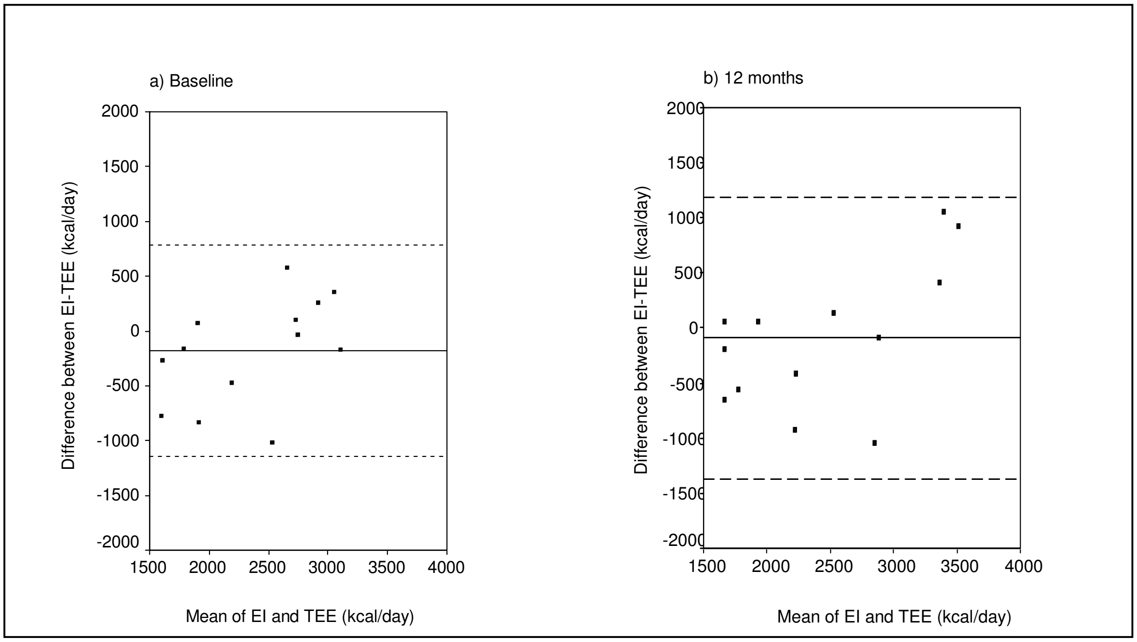

Figure 7. Bland-Altman plots: the difference between EI and TEE plotted against the mean of EI and TEE at (a) baseline and at (b) 12 months. —— Mean, ------ plus or minus two SD.

Study B *(paper III)*
Reported energy intake (kcal/kg/d), energy intake/REE or energy density was not predictive of changes in body weight at any time point.

Skeletal muscle mass

Study B *(paper IV)*
Preoperatively 13 out of 27 men (48%) and 1 out of 14 women (7%) were classified as sarcopenic [135].

Average TBSMM decreased significantly at 6 months postoperative but this loss was regained 6 months later. Changes in body weight were significantly associated with changes in TBSMM, but only for men when analysed by subgroups. Weight losers lost TBSMM during the first year as opposed to weight stable group.

Functional capacity

Study B *(paper IV)*

Although there was a reduction in exercise capacity at 6 months, no change from preoperative values was evident at 12 months postoperatively. Analyzed by subgroups it was found that men showed a trend to reduction and weight losers reduced their exercise capacity at 6 months but exercise capacity was restored in both groups at 12 months postoperatively.

TBSMM was related to exercise capacity at all time points, and in both genders, and for weight losers and weight stable (table 8). Changes in TBSMM predicted changes in exercise capacity and this applied to men, women and the weight stable group but not in the weight losing group (figure 8). Changes in body weight predicted changes in exercise capacity but analyzed by subgroups this applied only for men.

Table 9. Correlations between total body skeletal muscle mass (TBSMM) according to Kim (5) and exercise capacity at all times and in weight losing and weight stable and in both genders.

Correlation coefficient and significant level	$TBSMM_{pre}$-Exercise $capacity_{pre}$ (W)	$TBSMM_{6m}$- Exercise $capacity_{6m}$ (W)	$TBSMM_{12m}$- Exercise $capacity_{12m}$ (W)
Total	$0,70^{***}$	$0,69^{***}$	$0,61^{***}$
Weight losers	$0,74^{***}$	$0,69^{*}$	$0,61^{**}$
Weight stable	$0,60^{*}$	$0,70^{*}$	$0,59^{(*)}$
Men	$0,85^{***}$	$0,81^{***}$	$0,71^{***}$
Women	$0,66^{*}$	$0,57^{*}$	$0,59^{*}$

$^{(*)}$ borderline significant p=0.05-0.10, $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$

At the time of inclusion, both men and women in our study had lower exercise capacity compared to a Swedish reference population of healthy middle aged individuals (age 60-74) measured with the same protocol on the same treadmill [136].

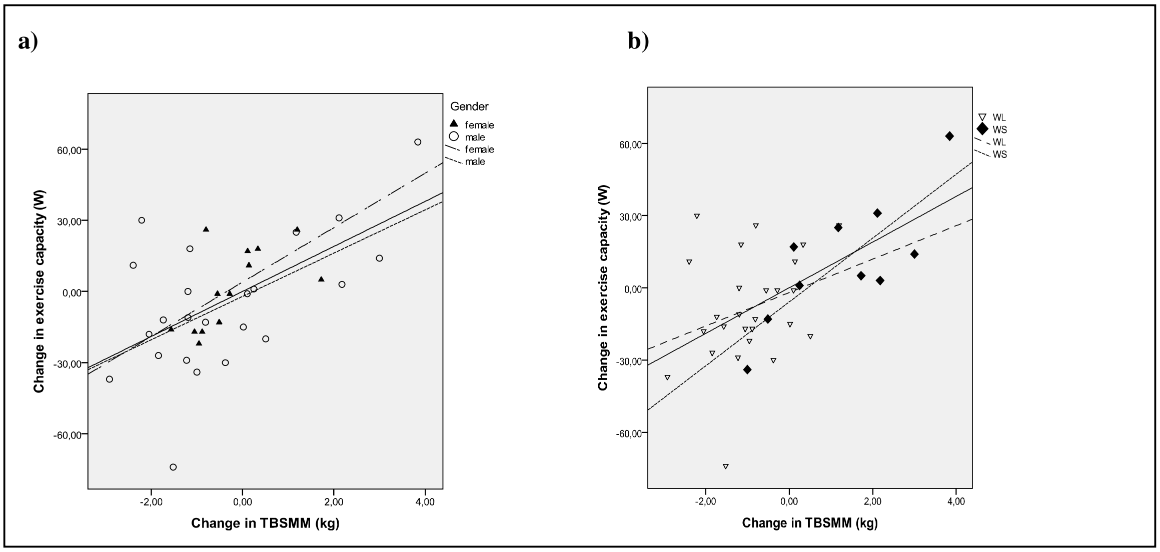

Figure 8. Correlations between change in exercise capacity during the first postoperative year and a) change in total body skeletal muscle mass (TBSMM); whole group n=36 r=0.58, p<0.001, men n=23 r=0.57, p<0.01, women n=13 r=0.62, p<0.05) and b) change in TBSMM; WL n=26 r=0.29 p=0.15, WS n=10 r=0.80 p<0.01.

Additional data analysis in Study A

From available hospital records the weight development preoperatively to one year after surgery (range 4 months to 1½ year) were identified and patients were classified as weight stable or weight losing in accordance with study B. Four patients (29%) were classified as WS and 10 (71%) patients were classified as WL.

Preoperative weight change in the WS group was -8.3 (4.6) % and -3.8 (4.4) % in the WL group, p=0.13.

On average 10 years after surgery 8/10 patients were still classified as weight losing whereas 3/4 were still weight stable (weight development from preoperative weight to weight at inclusion of study A). Long-term weight development, on average 10 years after surgery, in the weight stable group was 1.1 (10.2) kg (range -5.3 to 16.2 kg) and in the weight losing group -9.2 (7.5) kg (range -22.1 to 4.1 kg), p=0.06.

Weight stable patients had at the time for inclusion in study A a significantly higher FFMI (18.6 (0.7) vs 15.8 (2.0) kg/m^2, p=0.02) and appendicular skeletal muscle mass index (7.1 (0.7) vs 5.8 (1.0) kg/m^2, p=0.045) although there were no difference in weight (75.3 (3.0) vs 62.4 (14.0) kg, p=0.10. The weight stable group had also a significant higher exercise capacity as compared to weight losing (145 (35) vs 87 (28) watt, p=0.006). Two of the 4 weight stable patients were classified as sarcopenic, whereas 8 patients in the weight losing group were classified as sarcopenic (p=0.52).

On average 10 years after surgery 7 out of 10 men (70%) and 3 out of 5 women (60%) were classified as sarcopenic according to reference values defined as ≥2 SD below the appendicular skeletal muscle mass index of a young reference population [135].

DISCUSSION

The background to study A was the findings from a previously reported study of long-term survivors after total gastrectomy, at the Department of Surgery, Sahlgrenska Hospital [109]. This was a longitudinal study 5 to 8 years after surgery assessing weight and body composition changes. A loss of weight, greater than expected due to age, was found and also a significant loss of FFM. Oral nutritional therapy prescribed by a dietitian had been ended 5 years after surgery and the significance of nutritional surveillance in the long-term after TG was brought up. Thus, the overall aim of study A was to initiate oral nutritional therapy in a group of patients long time after TG, and evaluate its effects on body weight and body composition.

In the late 90s, at the time when study A was planned, little was known about physical activity energy expenditure in disease and also the applicability of different methods to measure physical activity in the home environment. We had the opportunity to use the DLW method, but since it is a very expensive method that requires advanced technical equipment and skills it is not applicable in routine care. Therefore, we also examined the validity and usability of simpler devices, such as ActiReg® and $HPAQ_{modified}$.

In Study B we investigated development of body weight and body composition during the first year after surgery. As in study A, body composition was measured with DXA and since the time when both these studies were originally designed, the knowledge on how to use DXA body composition measurements for calculations of body energy content and skeletal muscle mass had evolved. This made it possible to quantify energy balance, assess muscle mass and investigate the relationship between muscle mass and functional capacity.

Since we had revealed a lack of details in the method descriptions for oral nutritional therapy in the literature, one specific aim in both studies were to describe the oral nutritional therapy in detail.

Methodological considerations

Subjects

The common feature of all study patients was that they all had undergone major upper gastrointestinal surgery. As patients were included consecutively they naturally differed in many aspects such as gender, age, nutritional, social, marital and general health status. These, and maybe other differences not measured, most probably affected the response to surgery and nutritional therapy.

Study A
Our aim was to include 20-25 patients. However, because of the high tumour recurrence rate and a high mean age at diagnosis, the eligible number of patients 5 years after surgery was very limited. Based on clinical experience that most patients do not recover their pre-illness weight it was decided to include 5 patients who did not fulfil the inclusion criteria of a weight loss ≥5% compared to preoperative weight. There was no inclusion criterion for BMI. This resulted in that 4 of the 5 patients with a weight loss <5% also had a BMI close to (24.5) or more than 25. Two of these patients, although motivated in the beginning of the study, expressed later on a satisfaction with their weight. This underlines the importance of a thorough assessment to identify patients who most likely will benefit from nutritional therapy aiming to prevent loss of or to restore body mass.

Study B
This was a relatively large single centre study, in which ultimately 80 patients were operated and randomized. Due to the severity of the malignant disease more than 30% of the patients were lost due to incurable or recurrent disease, or died. 14% declined further participation or were lost for follow up but only 4% failed to meet our inclusion criterion of repeated DXA measurements. Thus, our group of patients should be representative of patients surviving the first postoperative year after curatively intended upper gastrointestinal cancer surgery.

The study included patients with different kinds of upper gastrointestinal disease which called for different kinds of resection procedures. As the oral nutritional therapy was symptom-based and since many of these patients do experience the same kind of symptoms we do not see this as a major issue.

Study design
One major drawback of these two studies is the absence of a control group. This renders it difficult to interpret the results since we do not know whether a change is due to nutritional therapy or other causes. Since the 80s oral nutritional therapy to this patient group is seen as a part of basic care at the hospital, and it would neither be feasible nor ethical appropriate to have “no nutrition” as the control.

Both studies shared the same protocol for how often the patients met the dietitian. During the first six months follow-up was based on regular meetings. This offered the possibility to do a proper re-assessment of nutritional and general health status and monitor and evaluate the prescribed nutritional therapy.
However, during the last 6 months of the studies patients and dietitian communicated over the telephone. The experience from study A was that the lack of a personal meeting hampered the monitoring of the nutritional therapy since not seeing the patient made it more difficult to reassess and adjust nutritional therapy to new circumstances.

Dietary intake

Energy intake was assessed by a 4D FR as the method was easy and not too time-consuming. To reduce reporting error, much effort was put in careful instructions to the patients on how to record. After the recording period the dietitian and patients met and any ambiguities in the record could be clarified. However, there were large individual discrepancies between energy intake from 4D FR and TEE from DLW. Although measured at the same time period during the study, the length of the measurement period differed. DLW was a mean value of 14 days whereas 4D FR obviously was a mean of 4 days. A variation in energy intake of 20-30 % between different days has been reported [72]. In the present studies this variation can be even greater since a majority of patients after MUGI surgery suffer from eating-related symptoms [3] and there is a risk for a 4D FR to miss this variation.

In study B we found that energy intake expressed as kcal/kg not at any time predicted changes in body weight. However, change in body weight was measured over a time period of at least one month so once again the discrepancy can be due to different time periods studied with regard to energy intake and body weight.

Body composition

DXA is a precise method to estimate body composition. Regional body composition is also estimated with adequate precision using DXA (although somewhat less than for total body composition). Coefficient of variation for BF was 1.7%, for lean soft tissue 0.7%, and for appendicular lean soft tissue 2.7%. Body energy content was estimated with a coefficient variation of 1.02%. Thus, over a period of 6 months, the error of measurement was approximately 16 kcal per day, corresponding to ~1% of an average daily intake.

Results in perspective

Preoperative nutritional state, body composition and functional capacity

Study B showed that 90% of the patients had a preoperative BMI >20. Since almost half of the patients had lost more then 10% of their pre-illness weight, BMI was not an indicator of nutritional deficit. Both BF and FFM were affected since our patients had significant lower levels as compared to a Swedish reference material [134].

The most striking finding preoperatively was low appendicular skeletal muscle mass. This might have been caused either by preoperative weight loss, or by tumour induced stress metabolism, or by low physical activity. There has been a lack of Swedish data on reference values for muscle mass, however in 2009 Tengvall et al [137] reported indices of TBSMM in 75-year old subjects. Still, to my knowledge the only existing DXA derived cut off values for sarcopenia is based on data from Baumgartner et al [135]. One third of our patients, mainly men, could be classified as sarcopenic according to these cut-off values. From the Baumgartner study [135] the reported prevalences of sarcopenia in non-hispanic white men and women age <70 years were 14% and 23%, and in the age group 70-74, 20% and 33% respectively. Compared to these data the prevalence of sarcopenia in our study was higher in men (48%) but lower in women (7%).

Sarcopenia has been associated with functional impairment [135,138] and functional impairment has actually been included in a recent definition of sarcopenia [139]. Our patients had a reduced maximal exercise capacity compared to a middle-aged reference population measured on the same treadmill [136]. Also, patients classified with sarcopenia had a significantly lower exercise capacity compared to patients with normal appendicular muscle mass indices.

Energy metabolism

Measurements of TEE from DLW revealed a great spread. TEE ranged from 31-44 kcal/kg. In accordance to this physical activity level varied within a wide range. This underlines the importance of individual assessment of energy requirements for patients receiving nutritional therapy and above all, a careful monitoring to evaluate the nutritional therapy and prescribed energy intake.

Postoperative nutritional state and body composition

The greatest postoperative weight loss occurred within the first month after surgery and persisted during the 12 months study. Six months after surgery more than 1/5 of average body fat stores were lost, but there was no significant change in fat-free mass. Unfortunately, there was no measure of body composition after the first postoperative month so we do not know to what extent the different body compartments were affected. However, due to the surgical stress response metabolism losses of FFM can be expected adjacent to surgery and this has been verified in a few studies on body composition following MUGI surgery [140-142].

Perhaps the most striking finding was the heterogeneity in weight development after surgery. Almost one third of the patients remained weight stable with even a gain in FFM 12 months after surgery. This was opposed to the weight losing group who lost some FFM, but almost 90% of the lost body mass was BF. This indicates an energy balance problem due to a reduced intake rather than a prolonged catabolic effect.

We found no preoperative variables that could explain this difference in postoperative recovery except that weight stable patients reported a higher preoperative weight loss. This is consistent with the finding of Martin et al [143] where an increased preoperative weight loss was associated with a decreased risk of weight loss after oesophageal and cardia cancer surgery. Martin et al suggested that patients with a greater preoperative weight loss received more nutritional attention after surgery. However, in our study all patients received individualized dietary counselling prescribed by a dietitian, which makes this explanation less likely in our patients. Also, we could not relate preoperative nutritional status as assessed by BMI to postoperative weight development.

From the extended analysis in study A it seems likely that patients classified as weight stable during the first postoperative year still had higher FFMI, appendicular skeletal muscle mass index and functional capacity long time after surgery. Although patients in study A are too few to draw any conclusions, it is an interesting observation that could be subject to further studies. We can only speculate that weight stable patients do better in the long run but the reasons why some patients lose weight while others don't remain to be explored.

Contrary to our anticipations nutritional therapy long time after surgery did not change body weight or body composition. However, also in this group of patients effects on body weight and body composition were heterogeneous. About half of the patients increased their body weight during the intervention year, and BF accounted for this gain in body mass. The other half of patients remained weight stable and co-morbidity had a great impact on weight development.

Skeletal muscle mass and functional capacity

Although TBSMM was regained at 12 months there was no further recovery of the preoperative low muscle mass. Long time after TG two thirds of the patients in study A were classified as sarcopenic [135] indicating a further muscle mass loss over time.

Change in TBSMM was related to change in body weight but analyzed by subgroups this was only significant in men but not in women, weight losing and weight stable. Maybe, men and women respond differently in degree of muscle mass changes in relation to how weight changes. However, these results must be interpreted cautiously as there were few women, and also small changes in TBSMM. The lack of relationship in the weight losing and weight stable groups could possibly be explained by the fact that both men and women were represented in each group.

We found a clear relationship between TBSMM and functional capacity measured as exercise capacity. We also found a relationship between changes in exercise capacity and changes in TBSMM. This indicates that development of TBSMM has a major impact on functional capacity.

Energy balance

The magnitude of the average energy deficit as measured from differences in body energy content might be overcome by oral intake. Worth mentioning is that we have measured gross energy balance, which can not be directly translated to energy intake. Factors of importance are 1) changes in body mass (weight) affect energy requirements, 2) approximately 5% of food energy is normally not absorbed, also some of these patients has an additional malabsorption caused by surgery, 3) to what extent extra energy intake is stored as body mass depends on how much of the extra energy is used as physical activity energy. This means that the energy intake to overcome the calculated energy deficit based on change in body energy content must be somewhat higher. In addition, all of these patients already received nutritional therapy to optimise energy intake. To further increase energy intake, nutritional therapy strategies probably must be reconsidered.

We could not find a linear relationship between energy balance and exercise capacity. However, the weight losing group had a significantly higher proportion of patients who reduced their exercise capacity compared to the weight stable group. This much more complex relationship requires additional studies.

Physical activity and physical activity energy

Both ActiReg® and $HPAQ_{modified}$ were found to underestimate TEE compared to DLW. The underestimation was seen at higher physical activity levels while on lower levels, especially ActiReg®, gave an impressively accurate measure of energy expenditure.

This is supported by other validation studies of ActiReg®. In the study of Hustvedt -who developed the equipment- et al [125] in a group of young female students, ActiReg® was found to give an accurate measure of TEE on group level although with a standard deviation of 320 kcal/day. On higher levels of energy expenditure (>2600 kcal/day), ActiReg® underestimated to a greater extent. The female students reached a PAL of 1.71. In the study of Arvidsson et al [144] in a group of non-hospitalized patients, suffering from severe chronic obstructive pulmonary disease, ActiReg® gave a valid estimate of TEE from ActiReg®, with a standard deviation of 190 kcal/day. However, PAL in this group was only 1.51. Based on these results it can be concluded that the ActiReg®-system is well adapted to assess TEE at lower levels of physical activity whereas at higher levels there is a great spread in individual difference between ActiReg® and DLW.

As opposed to $HPAQ_{modified}$, ActiReg® showed a variation comparable to DLW in estimation of TEE changes over time. This is a very interesting finding since this measure might be used to assess functional outcome after nutritional intervention. However, this requires further studies since TEE did not change in our study.

Up to date no validation study of motion sensors has proven a high enough precision in the estimate of total energy expenditure/physical activity energy expenditure at the individual level [54,145]. If nutritional therapy results in a more ambulatory patient, a more patient-centred outcome measure might be the ability of ActiReg® to estimate time spent in different body positions and activity levels.

The physical activity interview was difficult to perform and relied heavily on the patients' memory. In relation to the workload and the difficulties with the interviews, the clinical usefulness of this method seems limited. Other validation studies of physical activity questionnaires against DLW show generally low correlations with both under- and overestimates or agreement at the group level but with considerable error on the individual level [124].

Oral nutritional therapy

In study A we used the 4D FR to evaluate and re-assess oral nutritional therapy. Based on food choices and meal pattern it seemed as they followed previously prescribed diet recommendations. Energy density of the diet is primarily affected by the fat and water content. The reported energy density of 0.97 kcal/g seems to be somewhat higher compared to the findings of other studies [146,147] which also support the view that they still ate a diet high in fat. However, many patients had problem to increase their food intake due to symptoms commonly seen in gastrectomized patients, and thereby to reach their energy needs to achieve a weight gain. Therefore, a majority of the patients were prescribed ONS.

However, energy intake and number of eating occasions were unchanged at the end of the study. This implies that ONS suppressed ordinary food intake since reported compliance to prescription of ONS was good. It has earlier been recognized that long term use of ONS can led to suppression of food intake [1]. It could also be the case that under some circumstances e.g. illness, some of these patients found it easier and more convenient to use ONS than to prepare a meal. We do not know, but if this is the case ONS still fulfilled its purpose to increase energy and nutrient intake.

SUMMARY OF STUDY RESULTS

In this thesis the focus has been on the short and long-term effects on energy balance, body composition and functional capacity in patients on oral nutritional therapy after major upper gastrointestinal surgery.

The main findings are summarized as follows:

Preoperative nutritional status shows a BMI within the normal range for the majority of patients and this is also found long time after surgery. However, BMI, BFI and FFMI were low compared to a Swedish reference population. Almost half of the patients lost >10% of their body weight and one third were classified as sarcopenic.

The greatest weight loss after major upper gastrointestinal surgery occurred within the first postoperative month and then persisted during the subsequent year. This weight loss is not regained even long time after surgery, since in the group of TG patients, there was still a weight loss of 6% compared to preoperative weight on average 10 years postoperatively.

Nearly 90% of the lost body mass during the first postoperative year consisted of body fat whereas fat free mass was not significantly changed. Total body skeletal muscle mass was reduced 6 months after surgery, but was regained at 12 months. Total body skeletal muscle mass most probably do not ever reach normal values since two thirds of the patients in study A were sarcopenic on average 10 years after surgery.

There was a great heterogeneity in weight development. One year after surgery two thirds of the patients had lost weight and one third remained weight stable. In the weight losing group both body fat and fat-free mass were significantly reduced and in the weight stable group there was no significant change in body fat but a gain in fat-free mass. Neither BMI, REE, energy intake nor length of artificial nutrition support could explain these differences in weight development. However, the weight stable group reported a higher preoperative weight loss.

Although oral nutritional therapy did not change body weight, body composition or energy metabolism in the group of patients long time after total gastrectomy, the responses were quite heterogeneous. About half of the patients responded with weight gain while in the other half weight was either lost or did not change. Co-morbidity appeared to have a negative effect on body weight development while a satisfaction with body weight was expressed when BMI >25 and weight loss (compared to pre-illness weight and) since the time of surgery was less than 5%.

Measures of TEE by DLW showed a great variation in physical activity levels. Although both ActiReg® and $HPAQ_{modified}$ were correlated with TEE from DLW there was an underestimation of TEE. Underestimation was particularly detected at higher levels of physical activities. ActiReg® showed a high validity to measure change in TEE over time as opposed $HPAQ_{modified}$. However, results need to be confirmed in further studies since there was no average change in TEE in this study.

CONCLUSIONS AND FUTURE PERSPECTIVES

Our results highlight the need for a standardized NCP in which a meticulous assessment of the individual patient is undertaken aimed to decide on proper nutrition diagnose and adequate nutritional therapy, further for evaluation of individual goals that should be achieved by the prescribed nutritional therapy.

We found that BMI on its own was not a good predictor of nutritional status in our patients, both before and after major upper gastrointestinal surgery. A BMI within normal range can have been preceded by a major weight loss. Also a BMI within normal range can coexist with a reduced muscle mass which we found was directly related to functional capacity. There was also a wide range in physical activity levels and thus a wide range in energy requirements. Heterogeneity in weight development also stresses the importance of a careful assessment/reassessment of patients to allocate most resources to those most in need.

Monitoring and reassessment of oral nutritional therapy was hampered by not directly meeting the patients during the last six months of the study. The frequency of dietary counselling and also the balance between direct meetings and telephone contacts must be thoroughly considered.

Development of methodology

Registration of food intake and appetite

The large day-to-day variation in patients' food intake, from good days, when dietary intake is adequate, to bad days, when the intake may be almost non-existent, makes the traditional registration of dietary food intake by a 4D FR unsatisfactory. The method only records a few days compared to, as in this case, a one year long intervention. To obtain a more representative measure of food intake during the period of study, different methods can be discussed.

Retrospective methods are intended to reflect past food intake of varying length. However, the intention of these methods is to capture habitual food intake and fluctuations in food intake is probably impossible to detect. Retrospective methods are dependent on the memory of the recipient and the fluctuation in food intake due to good and bad days is probably more difficult to assess by these methods.

If the goal is to understand the pattern of appetite and eating behaviour and how this interacts with weight development, maybe a different approach should be evaluated. To be able to follow changes in food intake during a longer period an everyday simple notation of estimated intake during the day could be of more value and better capture the variation in food intake instead of trying to assess the absolute amount of energy and nutrients. Further, there is a need for development of scales for rating appetite to mirror how self perceived appetite varies and develops.

Development of oral nutritional therapy

There is a great need to develop methods that makes it possible to objectively evaluate nutritional therapy. The general lack of method descriptions or definitions of oral nutritional therapy is an obstacle. "Dietary counselling" and "dietary advice" are often used interchangeable, without descriptions or definitions. This complicates and precludes evaluation and interpretation of result, comparison of results between studies and the possibility to repeat studies.

There is no structure for how central concepts and terms in the field of nutrition therapy are oriented to each other and there is no consensus on definition of the terms used. This complicates the process of describing and evaluating nutritional therapy. During the time it took to complete this thesis, I made a journey towards a more conscious way to use expressions and terms. One example is how the concept of oral nutritional support was used. From the beginning, I used it as a generic term for "the whole package" that a dietitian can offer but without a definition. Now it has been replaced by oral nutritional therapy which is the overarching concept of diet therapy and supplements (fig 2, page 20). Using a standardized nutrition language and a common approach and framework for nutritional therapy gives us the opportunity to do "good research" and move from experienced-based to evidence-based practice.

Body composition

The low FFMI before surgery and also the high frequency of sarcopenia both before but also long time surgery calls for the use of simple methods to identify these patients. Low FFMI is associated with longer hospital stay and sarcopenia is associated with functional impairment and disability. Easily applied methods for determination of skeletal muscle mass, like bioimpedance analysis, could be of potential clinical value for evaluation of the development of sarcopenia in these patients. This, however, requires further validation.

Interventions to restore and regain body mass and muscle mass

There is exciting new research indicating that eicosapentaenoic acid (EPA) might have immunomodulatory or moderating effects on inflammation, thereby reducing the degradation of lean body mass in patients after oesophageal cancer surgery [140].

The concept of ERAS (enhanced recovery after surgery) has been applied to colorectal surgery with success. However, due to nausea, delayed gastric emptying and the frequently used "nil-by-mouth" strategy the introduction of ERAS has been hampered in major upper gastrointestinal surgery. However, as shown by Suehiro et al, Lassen et al and Hur et al [114-116] no differences in morbidity were found instead it seems like “food-at-will” has several advantages.

Evidence from exercise intervention studies in cancer patients also shows preliminary positive physiological and psychological benefits from exercise, including preservation or increase in muscle mass, when undertaken during or after traditional cancer treatment [148]. However, the optimal exercise prescription remains so far unknown and may depend on cancer type, treatment modality and patient characteristics.

Finally, to optimize the effects on skeletal muscle mass of physical therapy the distribution and amount of protein intake can be considered. A recent review [149] recommends a consumption of 25-30 g high quality protein for each of three daily meals (1.0-1.2 g protein per kg and day) and to incorporate habitual exercise in close temporal proximity to these meals.

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REFERENCES

1. Stratton RJ, Green CJ, Elia M: Disease-related malnutrition : an evidence-based approach to treatment. Wallingford, CABI, 2003.
2. Elia M, Zellipour L, Stratton RJ: To screen or not to screen for adult malnutrition? Clin Nutr 2005;24:867-884.
3. Bragelmann R, Armbrecht U, Rosemeyer D, Schneider B, Zilly W, Stockbrugger RW: Nutrient malassimilation following total gastrectomy. Scand J Gastroenterol Suppl 1996;218:26-33.
4. Baldwin C, Weekes CE, Campbell KL: Measuring the effectiveness of dietetic interventions in nutritional support. J Hum Nutr Diet 2008;21:303-305.
5. Butterworth CE: The skeleton in the hospital closet. 1974. Nutrition 1994;10:435-441; discussion 435, 441.
6. Hill GL, Blackett RL, Pickford I, Burkinshaw L, Young GA, Warren JV, Schorah CJ, Morgan DB: Malnutrition in surgical patients. An unrecognised problem. Lancet 1977;1:689-692.
7. Isaksson B: How to avoid malnutrition during hospitalization? Hum Nutr Appl Nutr 1982;36:367-373.
8. Isaksson B, Hulten B, Nilsson U, Sandstrom B, Warnold I: [Malnutrition in the hospital: the physician should increase his interest for patients' nutritive condition and food habits]. Lakartidningen 1985;82:498-501.
9. Warnold I, Hultén, B., Philipson, H., Sjölin, K., Isaksson, B.: Guidelines for nutrition assessment and nutrition therapy in clinical practice. Lakartidningen 1983;80:3162-3165.
10. Howard P, Jonkers-Schuitema C, Furniss L, Kyle U, Muehlebach S, Odlund-Olin A, Page M, Wheatley C: Managing the patient journey through enteral nutritional care. Clin Nutr 2006;25:187-195.
11. Kinosian B, Jeejeebhoy KN: What is malnutrition? Does it matter? Nutrition 1995;11:196-197.
12. Allison SP: Malnutrition, disease, and outcome. Nutrition 2000;16:590-593.
13. Elia M: Guidelines for Detection and Management of Malnutrition. In Elia M (ed):Maidenhead, Malnutrition Advisory group (MAG), Standing Committee of BAPEN., 2000.
14. Soeters PB, Reijven PL, van Bokhorst-de van der Schueren MA, Schols JM, Halfens RJ, Meijers JM, van Gemert WG: A rational approach to nutritional assessment. Clin Nutr 2008;27:706-716.
15. Meijers JM, van Bokhorst-de van der Schueren MA, Schols JM, Soeters PB, Halfens RJ: Defining malnutrition: Mission or mission impossible? Nutrition 2010;26:432-440.
16. Jensen GL, Mirtallo J, Compher C, Dhaliwal R, Forbes A, Grijalba RF, Hardy G, Kondrup J, Labadarios D, Nyulasi I, Castillo Pineda JC, Waitzberg D: Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee. Clin Nutr 2010;29:151-153.
17. International statistical classification of diseases and related health problems : ICD-10. Geneva, World Health Organization, 2009.
18. National Centre for Classification in Health: Australian coding standards for I.C.D.-10-AM. In National Centre for Classification in Health (ed):Sidney, 2008.
19. Green SM, Watson R: Nutritional screening and assessment tools for use by nurses: literature review. J Adv Nurs 2005;50:69-83.

20. Kondrup J, Allison SP, Elia M, Vellas B, Plauth M: ESPEN guidelines for nutrition screening 2002. Clin Nutr 2003;22:415-421.
21. Weekes CE, Spiro A, Baldwin C, Whelan K, Thomas JE, Parkin D, Emery PW: A review of the evidence for the impact of improving nutritional care on nutritional and clinical outcomes and cost. J Hum Nutr Diet 2009;22:324-335.
22. Corish CA, Kennedy NP: Protein-energy undernutrition in hospital in-patients. Br J Nutr 2000;83:575-591.
23. Kyle UG, Genton L, Pichard C: Hospital length of stay and nutritional status. Curr Opin Clin Nutr Metab Care 2005;8:397-402.
24. Näringsproblem i vård och omsorg : prevention och behandling, SoS-rapport 2000:11. Stockholm, Socialstyrelsen, 2000.
25. McWhirter JP, Pennington CR: Incidence and recognition of malnutrition in hospital. Bmj 1994;308:945-948.
26. Norman K, Pichard C, Lochs H, Pirlich M: Prognostic impact of disease-related malnutrition. Clin Nutr 2008;27:5-15.
27. Mowe M, Bosaeus I, Rasmussen HH, Kondrup J, Unosson M, Rothenberg E, Irtun O: Insufficient nutritional knowledge among health care workers? Clin Nutr 2008;27:196-202.
28. American Dietetic Association: International dietetics and nutrition terminology (IDNT) reference manual: Standardized language for the nutrition care process. ed Second, Chicago, IL 60606-6995, USA, 2009.
29. Nutrition care process and model part I: the 2008 update. J Am Diet Assoc 2008;108:1113-1117.
30. Hiesmayr M, Schindler K, Pernicka E, Schuh C, Schoeniger-Hekele A, Bauer P, Laviano A, Lovell AD, Mouhieddine M, Schuetz T, Schneider SM, Singer P, Pichard C, Howard P, Jonkers C, Grecu I, Ljungqvist O: Decreased food intake is a risk factor for mortality in hospitalised patients: the NutritionDay survey 2006. Clin Nutr 2009;28:484-491.
31. Food and nutritional care in hospitals : how to prevent undernutrition : report and recommendations of the Committee of Experts on Nutrition, Food Safety and Consumer Protection. Strasbourg, Council of Europe Pub., 2002.
32. Findus special foods. Findus Sverige AB: Konsistensguide, 2008. In, http://www.findusfoodservices.se/filearchive/1/1892/SF_Konsistensguide_A4_sept_2007.pdf, 2008.
33. National Collaborating Center for Acute Care: Nutrition support in adults Oral nutrition support, enteral tube feeding and parenteral nutrition. In, National Collaborating Center for Acute Care at The Royal Collage of Surgeons of England, 35-43 Lincoln's Inn Fields, London, WC2A 3PE, February 2006.
34. Commission directive 1999/21/EC: Dietary foods for special medical purposes.
35. Nilsson Balknäs U, Andersen M: Mat och näring för sjuka inom vård och omsorg. Uppsala, Statens livsmedelsverk, 2003.
36. Weimann A, Braga M, Harsanyi L, Laviano A, Ljungqvist O, Soeters P, Jauch KW, Kemen M, Hiesmayr JM, Horbach T, Kuse ER, Vestweber KH: ESPEN Guidelines on Enteral Nutrition: Surgery including organ transplantation. Clin Nutr 2006;25:224-244.
37. Braga M, Ljungqvist O, Soeters P, Fearon K, Weimann A, Bozzetti F: ESPEN Guidelines on Parenteral Nutrition: surgery. Clin Nutr 2009;28:378-386.
38. Lochs H, Allison SP, Meier R, Pirlich M, Kondrup J, Schneider S, van den Berghe G, Pichard C: Introductory to the ESPEN Guidelines on Enteral Nutrition: Terminology, definitions and general topics. Clin Nutr 2006;25:180-186.
39. American Society for Parenteral and Enteral Nutrition (ASPEN) Board of Directors and Clinical Practice Committee: Definitions of Terms, Style and Conventions Used in

A.S.P.E.N Board of Directors- Approved Documents. In, http://www.nutritioncare.org/Library.aspx, 2009.
40. Swedish Association of Clinical Dietitians: Nutrition Terminology, DRF. In, htpp:/www.drf.nu/Etiska_papper/terminologi.pdf, 2009.
41. Baldwin C, Weekes Christine E: Dietary advice for illness-related malnutrition in adults. Cochrane Database of Systematic Reviews DOI: 10.1002/14651858.CD002008.pub3.
42. Ravasco P, Monteiro-Grillo I, Vidal PM, Camilo ME: Dietary counseling improves patient outcomes: a prospective, randomized, controlled trial in colorectal cancer patients undergoing radiotherapy. J Clin Oncol 2005;23:1431-1438.
43. Ravasco P, Monteiro-Grillo I, Marques Vidal P, Camilo ME: Impact of nutrition on outcome: a prospective randomized controlled trial in patients with head and neck cancer undergoing radiotherapy. Head Neck 2005;27:659-668.
44. Isenring EA, Capra S, Bauer JD: Nutrition intervention is beneficial in oncology outpatients receiving radiotherapy to the gastrointestinal or head and neck area. Br J Cancer 2004;91:447-452.
45. Olin AO, Osterberg P, Hadell K, Armyr I, Jerstrom S, Ljungqvist O: Energy-enriched hospital food to improve energy intake in elderly patients. JPEN J Parenter Enteral Nutr 1996;20:93-97.
46. Gall MJ, Grimble GK, Reeve NJ, Thomas SJ: Effect of providing fortified meals and between-meal snacks on energy and protein intake of hospital patients. Clin Nutr 1998;17:259-264.
47. Barton AD, Beigg CL, Macdonald IA, Allison SP: A recipe for improving food intakes in elderly hospitalized patients. Clin Nutr 2000;19:451-454.
48. Odlund Olin A, Armyr I, Soop M, Jerstrom S, Classon I, Cederholm T, Ljungren G, Ljungqvist O: Energy-dense meals improve energy intake in elderly residents in a nursing home. Clin Nutr 2003;22:125-131.
49. Wang ZM, Pierson RN, Jr., Heymsfield SB: The five-level model: a new approach to organizing body-composition research. Am J Clin Nutr 1992;56:19-28.
50. Andreoli A, Scalzo G, Masala S, Tarantino U, Guglielmi G: Body composition assessment by dual-energy X-ray absorptiometry (DXA). Radiol Med 2009;114:286-300.
51. Kim J, Wang Z, Heymsfield SB, Baumgartner RN, Gallagher D: Total-body skeletal muscle mass: estimation by a new dual-energy X-ray absorptiometry method. Am J Clin Nutr 2002;76:378-383.
52. Kim J, Heshka S, Gallagher D, Kotler DP, Mayer L, Albu J, Shen W, Freda PU, Heymsfield SB: Intermuscular adipose tissue-free skeletal muscle mass: estimation by dual-energy X-ray absorptiometry in adults. J Appl Physiol 2004;97:655-660.
53. Mahan LK, Escott-Stump S, Krause MV: Krause's food, nutrition, & diet therapy. Philadelphia, Pa., W. B. Saunders, 2004.
54. Westerterp KR, Plasqui G: Physical activity and human energy expenditure. Curr Opin Clin Nutr Metab Care 2004;7:607-613.
55. IDECG Working Group: The doubly-labelled water method for measuring energy expenditure. Technical recommendations for use in humans. In Prentice A (ed):Vienna, International atomic energy agency, 1990.
56. Goran MI, Peters EJ, Herndon DN, Wolfe RR: Total energy expenditure in burned children using the doubly labeled water technique. Am J Physiol 1990;259:E576-585.
57. Casper RC, Schoeller DA, Kushner R, Hnilicka J, Gold ST: Total daily energy expenditure and activity level in anorexia nervosa. Am J Clin Nutr 1991;53:1143-1150.
58. Macallan DC, Noble C, Baldwin C, Jebb SA, Prentice AM, Coward WA, Sawyer MB, McManus TJ, Griffin GE: Energy expenditure and wasting in human immunodeficiency virus infection. N Engl J Med 1995;333:83-88.

59. Heijligenberg R, Romijn JA, Westerterp KR, Jonkers CF, Prins JM, Sauerwein HP: Total energy expenditure in human immunodeficiency virus-infected men and healthy controls. Metabolism 1997;46:1324-1326.
60. Toth MJ, Gottlieb SS, Fisher ML, Poehlman ET: Daily energy requirements in heart failure patients. Metabolism 1997;46:1294-1298.
61. Toth MJ, Fishman PS, Poehlman ET: Free-living daily energy expenditure in patients with Parkinson's disease. Neurology 1997;48:88-91.
62. Poehlman ET, Toth MJ, Goran MI, Carpenter WH, Newhouse P, Rosen CJ: Daily energy expenditure in free-living non-institutionalized Alzheimer's patients: a doubly labeled water study. Neurology 1997;48:997-1002.
63. Moses AW, Slater C, Preston T, Barber MD, Fearon KC: Reduced total energy expenditure and physical activity in cachectic patients with pancreatic cancer can be modulated by an energy and protein dense oral supplement enriched with n-3 fatty acids. Br J Cancer 2004;90:996-1002.
64. Delikanaki-Skaribas E, Trail M, Wong WW, Lai EC: Daily energy expenditure, physical activity, and weight loss in Parkinson's disease patients. Mov Disord 2009;24:667-671.
65. Elia M: Insights into energy requirements in disease. Public Health Nutr 2005;8:1037-1052.
66. Caspersen CJ, Powell KE, Christenson GM: Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep 1985;100:126-131.
67. Ainsworth BE, Haskell WL, Leon AS, Jacobs DR, Jr., Montoye HJ, Sallis JF, Paffenbarger RS, Jr.: Compendium of physical activities: classification of energy costs of human physical activities. Med Sci Sports Exerc 1993;25:71-80.
68. Ainsworth BE, Haskell WL, Whitt MC, Irwin ML, Swartz AM, Strath SJ, O'Brien WL, Bassett DR, Jr., Schmitz KH, Emplaincourt PO, Jacobs DR, Jr., Leon AS: Compendium of physical activities: an update of activity codes and MET intensities. Med Sci Sports Exerc 2000;32:S498-504.
69. Energy and protein requirements : report of a Joint FAO/WHO/UNU Expert Consultation. Geneva, World Health Organization, 1985.
70. Trabulsi J, Schoeller DA: Evaluation of dietary assessment instruments against doubly labeled water, a biomarker of habitual energy intake. Am J Physiol Endocrinol Metab 2001;281:E891-899.
71. Hagman U: Riktlinjer för användning av kostregistreringsmetoder : Guidelines for the use of food record methods. Uppsala, Statens livsmedelsverk, 1991.
72. Bingham S: The dietary assessment of individuals; methods, accuracy, new techniques and recommendations. Nutr Abstr Rev 1987;57:705-742.
73. Standardisering av 24-timmarsintervju : Standardisation of 24-hour recall. Uppsala, Statens livsmedelsverk, 1986.
74. Hagman U, Rastas M: Riktlinjer för användning av livsmedelsfrekvensmetoder : Guidelines for the use of food frequency methods. Uppsala, Statens livsmedelsverk, 1989.
75. Hill RJ, Davies PS: The validity of self-reported energy intake as determined using the doubly labelled water technique. Br J Nutr 2001;85:415-430.
76. Schoeller DA: The energy balance equation: looking back and looking forward are two very different views. Nutr Rev 2009;67:249-254.
77. Elia M, Stratton R, Stubbs J: Techniques for the study of energy balance in man. Proc Nutr Soc 2003;62:529-537.
78. Wang Z, Pi-Sunyer FX, Kotler DP, Wielopolski L, Withers RT, Pierson RN, Jr., Heymsfield SB: Multicomponent methods: evaluation of new and traditional soft tissue mineral models by in vivo neutron activation analysis. Am J Clin Nutr 2002;76:968-974.

79. National Board of Health and Welfare: Cancer incidence in Sweden 2008. InStockholm, Socialstyrelsen, 2009:http://www.socialstyrelsen.se/publikationer2009/2009-2012-2001.
80. Parkin DM, Bray F, Ferlay J, Pisani P: Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.
81. World Health Organisation: Fact sheet N°297 Cancer,. In, February 2009:http://www.who.int/mediacentre/factsheets/fs297/en/index.html.
82. National Board of Health and Wellfare: Cancer i siffror : populärvetenskapliga fakta om cancer. InStockholm, Socialstyrelsen : Cancerfonden, 2009:http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/8348/2009-8126-8127_2009126127.pdf
83. National Board of Health and Welfare: Causes of Death 2007. InStockholm, Sweden, Socialstyrelsen, 2009:http://www.socialstyrelsen.se/Lists/Artikelkatalog/Attachments/8309/2009-8125-8318_200912518_rev.pdf.
84. Troidl H, Kusche J, Vestweber KH, Eypasch E, Maul U: Pouch versus esophagojejunostomy after total gastrectomy: a randomized clinical trial. World J Surg 1987;11:699-712.
85. Curran FT, Hill GL: Failure of nutritional recovery after total gastrectomy. Br J Surg 1990;77:1015-1017.
86. Bozzetti F, Bonfanti G, Castellani R, Maffioli L, Rubino A, Diazzi G, Cozzaglio L, Gennari L: Comparing reconstruction with Roux-en-Y to a pouch following total gastrectomy. J Am Coll Surg 1996;183:243-248.
87. Iivonen MK, Koskinen MO, Ikonen TJ, Matikainen MJ: Emptying of the jejunal pouch and Roux-en-Y limb after total gastrectomy--a randomised, prospective study. Eur J Surg 1999;165:742-747.
88. Iivonen MK, Mattila JJ, Nordback IH, Matikainen MJ: Long-term follow-up of patients with jejunal pouch reconstruction after total gastrectomy. A randomized prospective study. Scand J Gastroenterol 2000;35:679-685.
89. Hyltander A, Bosaeus I, Svedlund J, Liedman B, Hugosson I, Wallengren O, Olsson U, Johnsson E, Kostic S, Henningsson A, Korner U, Lundell L, Lundholm K: Supportive nutrition on recovery of metabolism, nutritional state, health-related quality of life, and exercise capacity after major surgery: a randomized study. Clin Gastroenterol Hepatol 2005;3:466-474.
90. Ryan AM, Healy LA, Power DG, Rowley SP, Reynolds JV: Short-term nutritional implications of total gastrectomy for malignancy, and the impact of parenteral nutritional support. Clin Nutr 2007;26:718-727.
91. Fein M, Fuchs KH, Thalheimer A, Freys SM, Heimbucher J, Thiede A: Long-term benefits of Roux-en-Y pouch reconstruction after total gastrectomy: a randomized trial. Ann Surg 2008;247:759-765.
92. Kight CE: Nutrition considerations in esophagectomy patients. Nutr Clin Pract 2008;23:521-528.
93. Rouvelas I, Zeng W, Lindblad M, Viklund P, Ye W, Lagergren J: Survival after surgery for oesophageal cancer: a population-based study. Lancet Oncol 2005;6:864-870.
94. Bachmann J, Heiligensetzer M, Krakowski-Roosen H, Buchler MW, Friess H, Martignoni ME: Cachexia worsens prognosis in patients with resectable pancreatic cancer. J Gastrointest Surg 2008;12:1193-1201.
95. Fuchs KH, Thiede A, Engemann R, Deltz E, Stremme O, Hamelmann H: Reconstruction of the food passage after total gastrectomy: randomized trial. World J Surg 1995;19:698-705; discussion 705-696.

96. Liedman B, Andersson H, Berglund B, Bosaeus I, Hugosson I, Olbe L, Lundell L: Food intake after gastrectomy for gastric carcinoma: the role of a gastric reservoir. Br J Surg 1996;83:1138-1143.
97. Liedman B, Andersson H, Bosaeus I, Hugosson I, Lundell L: Changes in body composition after gastrectomy: results of a controlled, prospective clinical trial. World J Surg 1997;21:416-420; discussion 420-411.
98. Jentschura D, Winkler M, Strohmeier N, Rumstadt B, Hagmuller E: Quality-of-life after curative surgery for gastric cancer: a comparison between total gastrectomy and subtotal gastric resection. Hepatogastroenterology 1997;44:1137-1142.
99. Takahashi S, Maeta M, Mizusawa K, Kaneko T, Naka T, Ashida K, Tsujitani S, Kaibara N: Long-term postoperative analysis of nutritional status after limited gastrectomy for early gastric cancer. Hepatogastroenterology 1998;45:889-894.
100. Liedman B, Bosaeus I, Hugosson I, Lundell L: Long-term beneficial effects of a gastric reservoir on weight control after total gastrectomy: a study of potential mechanisms. Br J Surg 1998;85:542-547.
101. Liedman B, Svedlund J, Sullivan M, Larsson L, Lundell L: Symptom control may improve food intake, body composition, and aspects of quality of life after gastrectomy in cancer patients. Dig Dis Sci 2001;46:2673-2680.
102. Adachi S, Inagawa S, Enomoto T, Shinozaki E, Oda T, Kawamoto T: Subjective and functional results after total gastrectomy: prospective study for longterm comparison of reconstruction procedures. Gastric Cancer 2003;6:24-29.
103. Nomura E, Isozaki H, Fujii K, Toyoda M, Niki M, Sako S, Mabuchi H, Nishiguchi K, Tanigawa N: Postoperative evaluation of function-preserving gastrectomy for early gastric cancer. Hepatogastroenterology 2003;50:2246-2250.
104. Kono K, Iizuka H, Sekikawa T, Sugai H, Takahashi A, Fujii H, Matsumoto Y: Improved quality of life with jejunal pouch reconstruction after total gastrectomy. Am J Surg 2003;185:150-154.
105. Olbe L, Lundell L: Intestinal function after total gastrectomy and possible consequences of gastric replacement. World J Surg 1987;11:713-719.
106. Bragelmann R, Armbrecht U, Rosemeyer D, Schneider B, Zilly W, Stockbrugger RW: Total gastrectomy: the influence of preserved duodenal transit and of pouch reconstruction on abdominal symptoms, nutrient assimilation, and medico-social functioning. Ital J Gastroenterol Hepatol 1997;29:228-236.
107. Bae JM, Park JW, Yang HK, Kim JP: Nutritional status of gastric cancer patients after total gastrectomy. World J Surg 1998;22:254-260; discussion 260-251.
108. Braga M, Molinari M, Zuliani W, Foppa L, Gianotti L, Radaelli G, Cristallo M, Di Carlo V: Surgical treatment of gastric adenocarcinoma: impact on survival and quality of life. A prospective ten year study. Hepatogastroenterology 1996;43:187-193.
109. Liedman B, Henningsson A, Mellstrom D, Lundell L: Changes in bone metabolism and body composition after total gastrectomy: results of a longitudinal study. Dig Dis Sci 2000;45:819-824.
110. Copland L, Liedman B, Rothenberg E, Bosaeus I: Effects of nutritional support long time after total gastrectomy. Clin Nutr 2007;26:605-613.
111. Tyrvainen T, Sand J, Sintonen H, Nordback I: Quality of life in the long-term survivors after total gastrectomy for gastric carcinoma. J Surg Oncol 2008;97:121-124.
112. Windsor JA, Hill GL: Weight loss with physiologic impairment. A basic indicator of surgical risk. Ann Surg 1988;207:290-296.
113. Lassen K, Dejong CH, Ljungqvist O, Fearon K, Andersen J, Hannemann P, von Meyenfeldt MF, Hausel J, Nygren J, Revhaug A: Nutritional support and oral intake after gastric resection in five northern European countries. Dig Surg 2005;22:346-352; discussion 352.

114. Suehiro T, Matsumata T, Shikada Y, Sugimachi K: Accelerated rehabilitation with early postoperative oral feeding following gastrectomy. Hepatogastroenterology 2004;51:1852-1855.
115. Lassen K, Kjaeve J, Fetveit T, Trano G, Sigurdsson HK, Horn A, Revhaug A: Allowing normal food at will after major upper gastrointestinal surgery does not increase morbidity: a randomized multicenter trial. Ann Surg 2008;247:721-729.
116. Hur H, Si Y, Kang WK, Kim W, Jeon HM: Effects of early oral feeding on surgical outcomes and recovery after curative surgery for gastric cancer: pilot study results. World J Surg 2009;33:1454-1458.
117. Nicklin J: Gastrointestinal cancer: developing an information booklet for patients. Nurs Stand 2009;23:35-40.
118. Bozzetti F, Gianotti L, Braga M, Di Carlo V, Mariani L: Postoperative complications in gastrointestinal cancer patients: the joint role of the nutritional status and the nutritional support. Clin Nutr 2007;26:698-709.
119. Heymsfield SB, Smith R, Aulet M, Bensen B, Lichtman S, Wang J, Pierson RN, Jr.: Appendicular skeletal muscle mass: measurement by dual-photon absorptiometry. Am J Clin Nutr 1990;52:214-218.
120. International Dietary Energy Consultancy Group: The doubly-labelled water method for measuring energy expenditure. Technical recommandations for use in humans. InVienna, International Atomic Energy Agency, 1990.
121. Black AE, Prentice AM, Coward WA: Use of food quotients to predict respiratory quotients for the doubly-labelled water method of measuring energy expenditure. Hum Nutr Clin Nutr 1986;40:381-391.
122. Weir JB: New methods for calculating metabolic rate with special reference to protein metabolism. J Physiol 1949;109:1-9.
123. Montoye HJ: Measuring physical activity and energy expenditure. Champaign, IL, Human Kinetics, 1995.
124. Westerterp KR: Assessment of physical activity: a critical appraisal. Eur J Appl Physiol 2009;105:823-828.
125. Hustvedt BE, Christophersen A, Johnsen LR, Tomten H, McNeill G, Haggarty P, Lovo A: Description and validation of the ActiReg: a novel instrument to measure physical activity and energy expenditure. Br J Nutr 2004;92:1001-1008.
126. Anderssen S, Damm F., Bjerkan K., Lövö A., Hustvedt B. : Registration of physical activity and energy expenditure:a validity control of a questionnaire. Med Sci Sports Exerc 20000;32:81.
127. Food and Agriculture Organization/World Health Organization/United Nations University: Energy and protein Requirements. World Health Organization Technical Report Series no. 724. In, Geneva: WHO, 1985.
128. Anderssen S, Damm F, Bjerkan K, Lövö A, Hustvedt B: Registration of physical activity and energy expenditure: a validity control of a questionnaire. Med Sci Sports Exerc 2000;suppl 32:81.
129. Borg GA: Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14:377-381.
130. Swedish National Food Administration: Matmallen (A Swedish portion-guide for estimation of consumed amounts of food. Uppsala, Sweden, Swedish National Food Administration, 1997.
131. Swedish National Food Administration: The Food Composition Table - Energy and Nutrient. Uppsala, Sweden, Swedish National Food Administration, 1993.
132. Expertgruppen för samordning av sjukhuskosten; National Food Administration: Mat på sjukhus: Råd och riktlinjer från ESS-gruppen. Uppsala, National Food Administration, 1991.

133. Lawrence W, Jr.: Nutritional consequences of surgical resection of the gastrointestinal tract for cancer. Cancer Res 1977;37:2379-2386.
134. Larsson I, Berteus Forslund H, Lindroos AK, Lissner L, Naslund I, Peltonen M, Sjostrom L: Body composition in the SOS (Swedish Obese Subjects) reference study. Int J Obes Relat Metab Disord 2004;28:1317-1324.
135. Baumgartner RN, Koehler KM, Gallagher D, Romero L, Heymsfield SB, Ross RR, Garry PJ, Lindeman RD: Epidemiology of sarcopenia among the elderly in New Mexico. Am J Epidemiol 1998;147:755-763.
136. Lindholm E, Brevinge H, Bergh CH, Korner U, Lundholm K: Relationships between self-reported health related quality of life and measures of standardized exercise capacity and metabolic efficiency in a middle-aged and aged healthy population. Qual Life Res 2003;12:575-582.
137. Tengvall M, Ellegard L, Malmros V, Bosaeus N, Lissner L, Bosaeus I: Body composition in the elderly: reference values and bioelectrical impedance spectroscopy to predict total body skeletal muscle mass. Clin Nutr 2009;28:52-58.
138. Janssen I, Heymsfield SB, Ross R: Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. J Am Geriatr Soc 2002;50:889-896.
139. Muscaritoli M, Anker SD, Argiles J, Aversa Z, Bauer JM, Biolo G, Boirie Y, Bosaeus I, Cederholm T, Costelli P, Fearon KC, Laviano A, Maggio M, Fanelli FR, Schneider SM, Schols A, Sieber CC: Consensus definition of sarcopenia, cachexia and pre-cachexia: Joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". Clin Nutr 2010;29:154-159.
140. Ryan AM, Reynolds JV, Healy L, Byrne M, Moore J, Brannelly N, McHugh A, McCormack D, Flood P: Enteral nutrition enriched with eicosapentaenoic acid (EPA) preserves lean body mass following esophageal cancer surgery: results of a double-blinded randomized controlled trial. Ann Surg 2009;249:355-363.
141. Barratt SM, Smith RC, Kee AJ, Mather LE, Cousins MJ: Multimodal analgesia and intravenous nutrition preserves total body protein following major upper gastrointestinal surgery. Reg Anesth Pain Med 2002;27:15-22.
142. Kiyama T, Mizutani T, Okuda T, Fujita I, Tokunaga A, Tajiri T, Barbul A: Postoperative changes in body composition after gastrectomy. J Gastrointest Surg 2005;9:313-319.
143. Martin L, Jia C, Rouvelas I, Lagergren P: Risk factors for malnutrition after oesophageal and cardia cancer surgery. Br J Surg 2008;95:1362-1368.
144. Arvidsson D, Slinde F, Nordenson A, Larsson S, Hulthen L: Validity of the ActiReg system in assessing energy requirement in chronic obstructive pulmonary disease patients. Clin Nutr 2006;25:68-74.
145. Plasqui G, Westerterp KR: Physical activity assessment with accelerometers: an evaluation against doubly labeled water. Obesity (Silver Spring) 2007;15:2371-2379.
146. Wallengren O, Lundholm K, Bosaeus I: Diet energy density and energy intake in palliative care cancer patients. Clin Nutr 2005;24:266-273.
147. Ledikwe JH, Blanck HM, Khan LK, Serdula MK, Seymour JD, Tohill BC, Rolls BJ: Dietary energy density determined by eight calculation methods in a nationally representative United States population. J Nutr 2005;135:273-278.
148. Hayes SC, Spence RR, Galvao DA, Newton RU: Australian Association for Exercise and Sport Science position stand: optimising cancer outcomes through exercise. J Sci Med Sport 2009;12:428-434.
149. English KL, Paddon-Jones D: Protecting muscle mass and function in older adults during bed rest. Curr Opin Clin Nutr Metab Care 2010;13:34-39.