From the Department of Clinical Science, Intervention and Technology (CLINTEC)
Division of Orthopedics and Biotechnology
Karolinska Institutet, Stockholm, Sweden

STUDIES ON HIP FRACTURE PATIENTS – EFFECTS OF NUTRITION AND REHABILITATION

Lena Flodin

Stockholm 2015

All previously published papers were reproduced with permission from the publisher.
Published by Karolinska Institutet.
Picture on cover drawn by Cecilia Flodin (bronze statue by Alberto Giacometti)
Printed by AJ E-print AB

ISBN 978-91-7549-894-2

Studies on hip fracture patients – effects of nutrition and rehabilitation

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Birkeaulan, Karolinska Universitetssjukhuset Huddinge

Fredagen den 8 maj, 2015, kl 10.00

By

Lena Flodin
Leg läkare

Huvudhandledare:
Docent Margareta Hedström
Karolinska Institutet
Institutionen för klinisk vetenskap, intervention och teknik
Enheten för ortopedi och bioteknologi

Bihandledare:
Professor Tommy Cederholm
Uppsala Universitet
Institutionen för folkhälso- och vårdvetenskap
Enheten för klinisk nutrition och metabolism

Adj professor Johan Lökk
Karolinska Institutet
Institutionen för neurobiologi, vårdvetenskap och samhälle
Enheten för klinisk geriatrik

Fakultetsopponent:
Professor Kristina Åkesson
Lunds Universitet
Institutionen för kliniska vetenskaper, Malmö
Enheten för klinisk och molekylär osteoporosforskning

Betygsnämnd:
Docent Ami Hommel
Lunds Universitet
Institutionen för hälsovetenskaper

Professor Matti Viitanen
Karolinska Institutet
Institutionen för neurobiologi, vårdvetenskap och samhälle
Enheten för klinisk geriatrik

Docent Olof Sköldenberg
Karolinska Institutet
Institutionen för kliniska vetenskaper, Danderyds sjukhus
Enheten för ortopedi

To all of you who have suffered a hip fracture.
The effort to improve treatment and care continues.

ABSTRACT

Hip fracture in the elderly is a serious condition associated with increased mortality. Survivors experience an increase in morbidity and disability that affect their independence and quality of life; the outcome for patients with dementia is particularly poor. Many hip fracture patients have signs of malnutrition already on admission and this patient group has been shown to have a lower body mass index (BMI) than aged-matched controls. A catabolic state develops following hip fracture, characterized by loss of bone mineral density (BMD) and muscle mass. The combination of generalized loss of muscle mass, muscle strength and/or physical performance is known as sarcopenia, which impacts functionality and health-related quality of life. This thesis has three major aims: 1) to study the possible association between BMI, a potentially modifiable factor, and one-year mortality, as well as the ability to return to independent living following hip fracture; 2) to evaluate the effect of nutritional supplementation on bone mineral density (BMD), body composition, muscle strength and health-related quality of life (HRQoL) following hip fracture; and 3) to investigate factors of importance for preservation of ambulatory function and activities of daily living (ADL) following hip fracture in patients with cognitive impairment.

Study I A prospective study of 843 elderly patients with hip fracture, without severe cognitive impairment, who came from an independent living situation at the time of admission. The results show that overweight was associated with increased one-year survival and a greater likelihood of independent living one year post-fracture.

Study II A randomized controlled study in which 79 patients with hip fracture were randomized to one of three treatment groups. Six months of postoperative treatment with protein and energy-rich supplementation combined with orally administered bisphosphonate, calcium and vitamin D were shown to have a small additive effect on bone mineral density compared with bisphosphonate and calcium alone.

Study III A randomized controlled study of the same population as in study II. Postoperative treatment with protein and energy-rich supplementation did not prevent loss of lean mass following hip fracture. However, trends toward improved handgrip strength and HRQoL were observed following nutritional supplementation.

Study IV A prospective study of 246 patients with femoral neck fracture and cognitive impairment, but ambulant prior to fracture. In addition to ambulatory and ADL function prior to fracture, the results showed that discharge to rehabilitation facilities was associated with preserved ambulatory function and ADL skills at the 4-and 12 month follow-ups.

LIST OF SCIENTIFIC PAPERS

I. Lena Flodin, Agnes Laurin, Johan Lökk, Tommy Cederholm, Margareta Hedström
Overweight in elderly hip fracture patients is associated with increased 1-year survival and discharge to independent living: a prospective study of 843 patients
In Manuscript

II. Lena Flodin, Maria Sääf, Tommy Cederholm, Amer Al-Ani, Paul Ackermann, Eva Samnegård, Nils Dalén, Margareta Hedström
Additive effects of nutritional supplementation, together with bisphosphonates, on bone mineral density after hip fracture: a 12-month randomized controlled study
Clinical Interventions in Aging 2014, 9: 1043-1050

III. Lena Flodin, Tommy Cederholm, Maria Sääf, Wilhelmina Ekström, Amer Al-Ani, Margareta Hedström
Effects of protein-rich nutritional supplementation and bisphosphonates on body composition, handgrip strength and health-related quality of life after hip fracture: a 12-month randomized controlled study
Submitted

IV. Amer Al-Ani, Lena Flodin, Anita Söderqvist, Paul Ackermann, Eva Samnegård, Nils Dalen, Maria Sääf, Tommy Cederholm, Margareta Hedström
Does rehabilitation matter in patients with femoral neck fracture and cognitive impairment? A prospective study of 246 patients Archives of Physical Medicine and Rehabilitation 2010, 91(1): 51-57

CONTENTS

LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
aLM	Appendicular Lean Mass
aLMI	Appendicular Lean Mass Index
ASA	American Society of Anesthesiologists
BMC	Bone Mineral Content
BMD	Bone Mineral Density
BMI	Body Mass Index
DXA	Dual Energy X-ray absorptiometry
FFM	Fat-Free Mass
FFMI	Fat-Free Mass Index
FM	Fat Mass
FMI	Fat Mass Index
HGS	Hand Grip Strength
HRQoL	Health-Related Quality of Life
RCT	Randomized Controlled Trial
sBMD	Standardized Bone Mineral Density
SD	Standard Deviation
SPMSQ	Short Portable Mental Status Questionnaire

1 BACKGROUND

1.1 HIP FRACTURE

1.1.1 Definition, anatomical classification and surgical treatment

Hip fracture is the general term for fractures located in the proximal part of the femur. The two most common types of hip fracture are those found in the femoral neck and in the trochanteric region, which account for about 51% and 38%, of hip fractures, respectively. The remainder comprise subtrochanteric and basocervical fractures [1]. In femoral neck fractures, surgical treatments generally include internal fixation with two screws or hip replacement. Trochanteric and subtrochanteric fractures are treated with dynamic hip screws or medullary nailing.

1.1.2 Epidemiology

In Sweden, with a population of 9.7 million, about 70 000 osteoporosis-related fractures occur each year and 26% of these are hip fractures [2]. Hip fractures are most common among the elderly, with a greater proportion of women (68%) [1]. The average age at fracture has been reported to be 83.8 years for women and 82.1 years for men [3]. Hip fractures in this age group usually occur indoors through low-energy impact such as a fall on the floor [4]. Hip fractures in the elderly population are serious because they often result in long-term functional impairment and loss of independence. Morbidity is high [5,6], and the mortality rate has been reported to be 3 to 5 times higher in women and 5 to 7 times higher in men during the first year after surgery [7,8]. Advanced age, male sex, poor general health and cognitive dysfunction are factors known to increase the mortality rate [9, 10-12].

1.1.3 Osteoporosis

Osteoporosis is characterized by low bone mass, expressed as bone mineral density (BMD). BMD is a mathematical ratio of the measured mineral content in a defined area of bone [13]. In addition to low BMD, osteoporosis is characterized by micro-architectural deterioration of bone tissue, leading to increased bone fragility and risk of fractures. The most validated technique to measure BMD is by dual energy X-ray absorptiometry (DXA). Based on measurement of BMD, osteoporosis is defined as a T-score of - 2.5 standard deviations (SD) below the average value for healthy young, women [14]. A normal BMD is defined as a T-score higher than -1 SD compared with the reference population. BMD decreases with age after reaching its peak between ages 20-30. The rate of bone loss accelerates in women during menopause. However, differences in the rate of bone loss between men and women decrease by age 65 [15]. Non-modifiable risk factors for osteoporosis include age, female sex and early

menopause (<47 years), as well as history of fracture, steroid treatment, ethnicity and family history.
However, there are also well known risk and lifestyle factors that can be influenced such as smoking, alcohol, a propensity to fall and low sun exposure [16]. In addition, underweight and poor nutritional status are potentially modifiable risk factors for osteoporosis and fracture.

1.1.4 Nutritional status, body mass index and biochemical markers of nutrition.

Optimal nutritional status entails stable weight with balanced energy intake and nitrogen production. Disruption of this balance will result in weight gain or loss. The general pattern of weight change over the course of life is weight gain up to approximately age 60 followed by weight loss. Body composition changes throughout life, but a slow increase of fat with age during adulthood has been described, though with great variability between individuals and the sexes [15]. Skeletal muscle mass is relatively stable until age 30 to 40, after which it begins to decrease with accelerated loss accompanying older age; the rate of loss is reported to be greater for leg muscle than for arm muscle [17]. Weight loss of 10% or more in the elderly is associated with a large risk of malnutrition [18]. One commonly used anthropometric marker of nutritional status is body mass index (BMI, kg/m²). This index is used to classify underweight (< 18.5), normal weight (18.5-25 kg/m²), overweight > 25 and obesity (≥ 30 kg/m²). The BMI ranges are set by the World Health Organization (WHO) to predict the impact of body weight on morbidity and mortality in young and middle-aged adults [19]. The European Society for Clinical Nutrition and Metabolism (ESPEN) has adjusted the threshold for people above age 65 and declared that a BMI of less than 20 is to be regarded as underweight or at risk of undernutrition [20]. The corresponding figure for people older than age 70, as set by the Swedish National Board of Health and Welfare, is a BMI of less than 22, which together with weight loss of 10% or more is defined as being malnourished [21]. A low BMI has been reported to be more common among patients with hip fracture compared with age-matched controls [22, 23], and a BMI of less than 22 kg/m² was found in about 25% of one hip fracture population [24]. A recent study showed that the prevalence of malnourishment among hip fracture patients was nearly 38% [25], while others have reported it to be between 15 and 33% [26, 24]. Despite changes in care through the years, many patients with hip fracture are still identified as being underweight based on their BMI. The association between BMI and outcome following hip fracture has not been fully explored.

Serum insulin-like growth hormone-I

Although an ideal biochemical marker for malnutrition does not exist, serum insulin-like growth hormone (IGF-I) may reflect nutritional status and IGF-I is known to respond to nutritional support [27]. IGF-I is a peptide hormone with anabolic effects on protein and carbohydrate metabolism, exerted through increased uptake of amino acids, thereby making it an important regulator of muscle mass [28]. Bone has also been shown to be another target for IGF-I [29]. IGF-I levels decrease in malnourished patients and increase in response to nutritional support [28]. IGF-I is mainly synthesized in the liver and production is regulated by growth hormone, gonadal steroids, thyroxine, cortisol, nutrition and genetic factors. The bioactive component accounts for less than 1% and the major proportion is bound to IGF binding proteins [30] Circulating IGF levels reach a maximum during peripubertal growth and gradually decline with age [31, 32]. The systemic actions of IGF-I are affected by metabolic disorders such as GH deficiency, acromegaly, obesity and diabetes [30]. IGF-I is also affected by trauma associated with hip fracture and a marked reduction has been reported after surgery[33].

Serum albumin

Serum levels of albumin may be subnormal in malnutrition [30]. However, as is true of all protein markers, levels must be interpreted with caution since they may be affected by several factors such as hydration status, liver function and especially by the acute phase response seen after hip fracture. Nevertheless, they are used to monitor nutritional support as a complement to other nutritional assessments [30].

1.1.5 Marker of bone resorption

C-terminal telopeptide of collagen-I (CTX-I)

Bone turnover is a continuous process of bone resorption and formation that occurs in localized areas known as bone remodeling units. Serum CTX-I, as a collagen degradation product, is one of the biochemical markers of bone resorption [34] that has been recommended for use in clinical practice and in research studies by the International Osteoporosis Foundation [35]. Serum levels of CTX exhibit diurnal variation with the highest values at night and the lowest in the afternoon. Other causes of variability are age, sex and a number of diseases, including primary hyperparathyroidism, Paget's disease, myeloma and chronic kidney disease. Following fracture and during fracture healing, serum CTX-I levels increase within two weeks and then remain elevated for up to one year compared with pre-fracture levels [36, 37]. Treatment with antiresorptive drugs such as bisphosphonates decreases CTX-I levels, which can therefore be used to monitor treatment compliance [35].

1.1.6 Sarcopenia

A decline in skeletal muscle mass is associated with the aging process [15]. Loss of muscle mass has been reported to be 1-2% yearly after age 50 [38]. After a hip fracture, the trauma itself, presurgical fasting and hip fracture-associated immobilization contribute to loss of muscle mass and strength. As much as 5-6% of muscle mass has been reported to be lost during the first year following fracture [39,40]. The current definition of sarcopenia is a combination of reduced muscle mass and muscle function (strength or physical performance) [41, 42]. Sarcopenia is associated with an increased risk of falls [43], and an impaired ability to remain independent in activities of daily living (ADL) [44]. Increased muscle wasting following hip fracture is likely to be one of several factors that influence poor outcomes such as impaired walking ability, ADL function [5], and deterioration in health-related quality of life (HRQoL) according to EuroQoL (EQ-5D) [45]. Sarcopenia is complex and the underlying mechanisms are multifactorial, including both morphological and functional changes in muscles. Factors that contribute to these changes include reduced physical activity, poor nutritional intake, genetic factors, inflammatory activity and a decrease in anabolic hormones [46]. The prevalence of low muscle mass measured by DXA has been reported at 20-85% in hip fracture patients, depending on age and sex [47, 48]. Studies on muscle mass together with muscle strength following hip fracture are lacking. Hand grip strength (HGS) as measured by a hand dynamometer is one method to assess muscle strength [41]. A strong association has been shown between HGS and leg muscle strength; HGS has also been shown to predict mobility better than muscle mass [49].

1.1.7 Nutritional supplementation, oral bisphosphonate and vitamin D

In order to maintain muscle mass in elderly there are recommendations for a higher daily protein intake, both in healthy individuals and in those who have acute or chronic diseases [50]. Voluntary food intake is often insufficient to meet the elevated protein and energy requirements following hip fracture surgery [26]. Oral nutritional supplements are recommended for elderly hip fracture patients [20]. One study showed that postoperative protein supplementation reduces proximal femur bone loss one year post-hip fracture [51]. A reduced postoperative complication rate [52], and a shorter length of hospital stay have also been shown by protein-rich oral nutritional supplementation [53]. However, the benefit of nutritional supplementation for hip fracture patients has not been conclusively demonstrated, as stated in a Cochrane Collaboration review [54] and few studies have been carried out concerning nutritional effects on bone mineral density and body composition as measured by DXA.

Adequate serum levels of calcium and vitamin D are important for bone metabolism, but this combination alone is not recommended for the treatment of osteoporosis due to the lack of evidence to support their ability to reduce fracture risk [55]. Vitamin D3 (cholecalciferol) has been reported to have preventive effects on falls [56], while vitamin D2 (ergocalciferol) has been shown to have a beneficial effect on muscle strength in older women with insufficient levels of serum-25OH-vitamin D [57]. Bisphosphonates reduce bone resorption and are widely used for primary and secondary prevention of osteoporotic fractures [58,59,60, 61,62]. An increase in total hip BMD has been reported after treatment with bisphosphonates in patients with a recent hip fracture [63].

1.1.8 Rehabilitation and cognitive impairment

Previous reviews describe strong evidence for the benefits of exercise programs for outcome regarding functional recovery, balance and muscle strength following hip fracture [64, 65]. Multidisciplinary rehabilitation following hip fracture has also been shown to improve outcome regarding mobility and ADL [66]. The prevalence of dementia or severe cognitive impairment has been reported in about 15 to 32% of hip fracture patients [67, 68]; a rough assessment of cognition can be made with the Short Portable Mental Questionnaire (SPMSQ)[69]. It has been shown that the presence of any kind of severe cognitive impairment, including delirium, detected during hospital stay, is a risk factor for poor outcome after hip fracture with influence on ADL, ambulatory capacity and mortality [11, 70, 71]. However, the presence of dementia does not preclude the restoration of baseline function following hip fracture [72]. Despite this knowledge are patients with dementia less likely to have the same training opportunities as cognitively intact individuals [5]. Preserved ambulatory function is one of several factors associated with health-related quality of life after hip fracture [45] and it is therefore important to identify factors that help to preserve this function.

2 AIMS

Study I

The primary aim was to investigate the association between body mass index and one-year mortality, while the secondary aim was to study the association between BMI and independent living one year postoperatively.

Study II

To evaluate the effect of postoperative treatment with calcium, vitamin D and bisphosphonate, alone or together with protein-rich nutritional supplementation, on total hip and total body BMD.

Study III

To evaluate the combined effects of protein-rich nutritional supplementation and bisphosphonate on body composition, handgrip strength and HRQoL.

Study IV

To explore factors associated with preservation of ambulatory function and ADL skills at 4 and 12 months postoperatively in patients with femoral neck fracture and cognitive impairment.

3 METHODS

3.1 PATIENTS, SETTINGS AND DESIGN

Charts of included patients in studies I-IV are shown below (Figure 1 and 2).

Figure 1 Chart of included patients studies I and IV

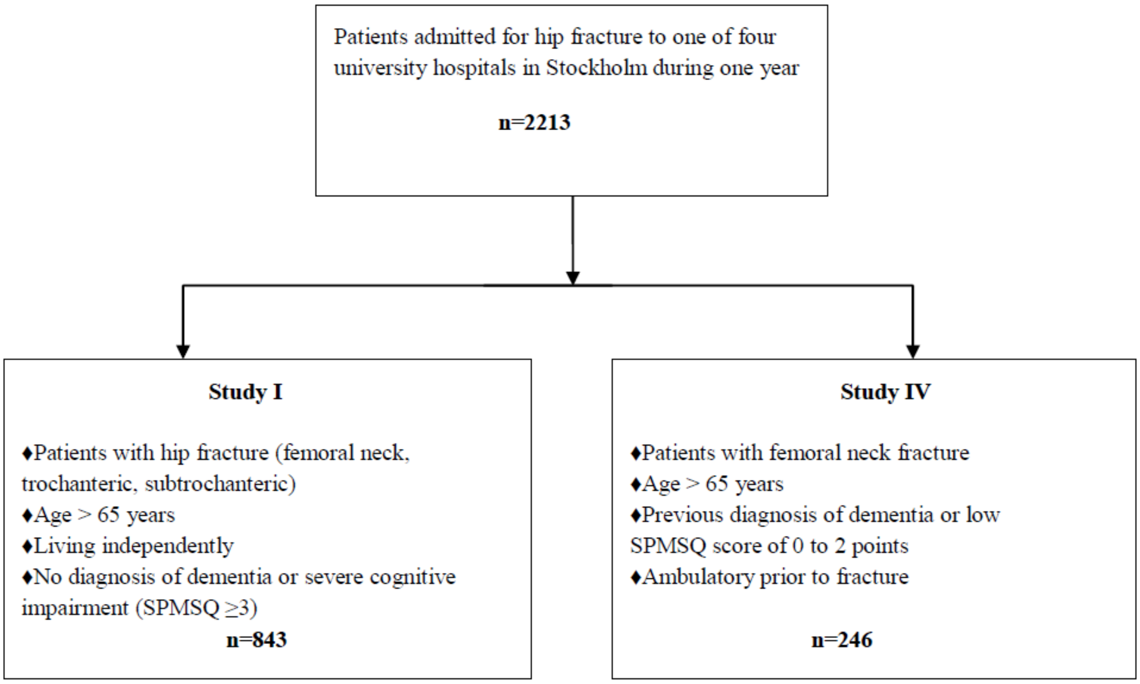
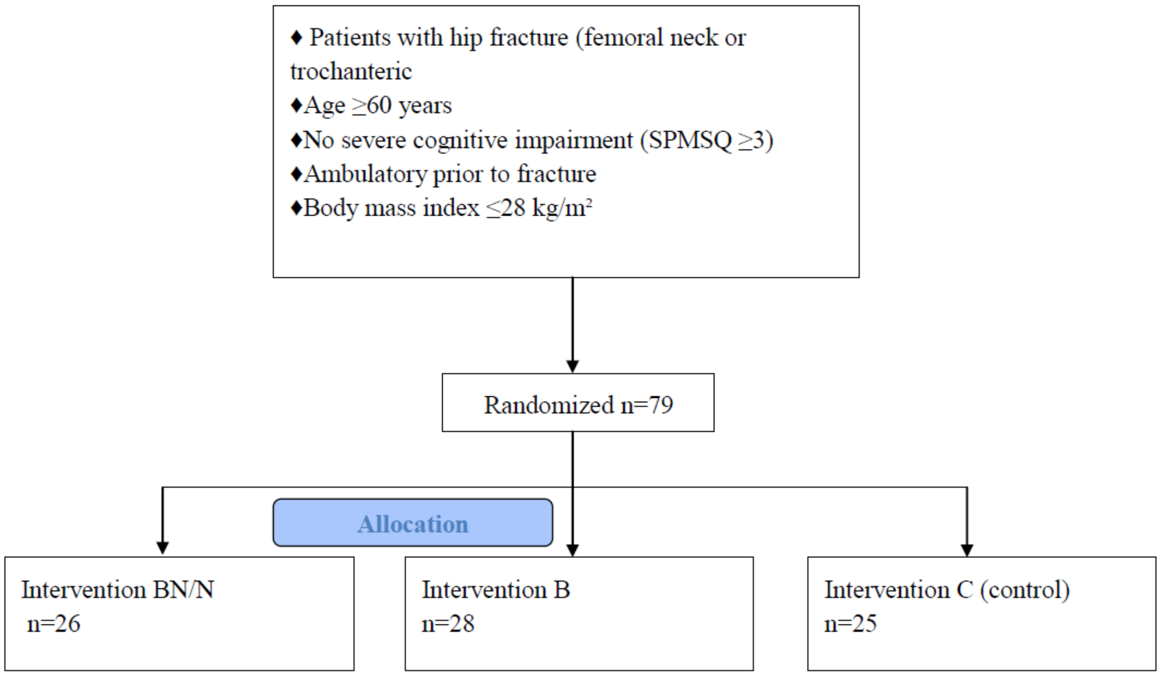


Figure 2 Chart of included patients studies II and III



Abbreviations: BN/N: bisphosphonate together with nutritional supplementation and calcium + vitamin D; B: bisphosphonate and calcium + vitamin D; C: controls treated with calcium + vitamin D

Study I

The population in this prospective study was derived from a Stockholm Hip Fracture Group Study and consisted of 843 patients with hip fracture (femoral neck, trochanteric or subtrochanteric), who were admitted to one of four University hospitals in Stockholm (Karolinska University Hospital, Huddinge; Karolinska University Hospital, Solna; Danderyd Hospital; and Stockholm South Hospital) during one year. Inclusion criteria were age >65 years, living independently and no diagnosis of dementia or severe cognitive impairment according to the Short Portable Mental Questionnaire (SPMSQ ≥3 correct answers).

Studies II and III

These studies built on a randomized, controlled, interventional trial in which the population used for study II and study III was the same and included 79 men and women with hip fracture (femoral neck or trochanteric) admitted to any of the four university hospitals in Stockholm, Sweden during 2005-2009. Study II focused on the outcome of bone mineral density and study III on body composition, handgrip strength and HRQoL. Inclusion criteria were: age ≥60 years, no severe cognitive impairment (SPMSQ ≥3), ambulatory prior to fracture, and body mass index (BMI) ≤28 kg/m2. Exclusion criteria were: treatment with bisphosphonate within the last year and pathological fracture, or patients with bone metabolic disorders such as primary hyperparathyroidism, osteogenesis imperfecta, Paget's disease or myeloma. Also excluded were patients with abnormal hepatic or renal laboratory parameters such as S-ALT, S-AST ≥ twice the normal reference range respectively, S-creatinine >130 µg/L or GFR <30 ml/min. Additional exclusion criteria were lactose intolerance, dysphagia, esophagitis, gastric ulcer or malignancy, diabetes mellitus associated with nephropathy or retinopathy, active iritis or uveitis, as well as patients with alcohol/drug abuse or overt psychiatric disorders.

Intervention studies II and III

Patients were randomized into three groups using sealed envelopes in blocks of 12. All patients received calcium (1000 mg) and vitamin D3 (800 IE) daily. The first group was randomized to treatment with bisphosphonates, risedronate 35 mg (Optinate® Septimum) once weekly for 12 months (n=28). The second group was treated with bisphosphonates along with daily nutritional supplementation (Fresubin® protein energy drink) for the first six months (n=26). The third group served as controls (n=25) and was treated with calcium and vitamin D alone (Calcichew-D3®) for 12 months. The nutritional supplement was a liquid formula and contained 150 kcal and 10 grams protein/100 ml with a balanced mix of micronutrients. The protein content was milk-based consisting of 80% casein and 20% whey. Patients were prescribed 200 ml twice daily of the liquid supplement.

Pharmacological treatment and nutritional supplementation began as soon as patients were stable from a cardiovascular standpoint, able to take food by mouth and able to sit in an upright position for one hour after taking their tablets. The research nurses interviewed patients by telephone regarding compliance, food intake, pain and general state of health.

Study IV

This was a prospective study of 246 patients aged > 65 years, with femoral neck fracture who were admitted to one of four university hospitals in Stockholm during one year. Included were patients with a diagnosis of dementia or severe cognitive impairment (SPMSQ 0 to 2 points), who were ambulatory prior to fracture.

3.2 DATA COLLECTION

Study I

Upon hospital admission hip fractures were classified by orthopedic surgeons, while anesthesiologists carried out a separate classification based on the American Society of Anesthesiologists (ASA) classification system [73] prior to surgery. At inclusion, patient data were recorded, including age, sex, type of fracture and surgical method, as well as pre-fracture Katz ADL index [74], use of walking aids and living situation. Research nurses assessed cognitive status according to the Short Portable Mental Status Questionnaire (SPMSQ) [69]. Weight measurements were obtained either using a bed scale on admission or postoperatively on a wheelchair scale. Height was measured in supine position. Body mass index (BMI) was calculated (kg/m^2). BMI levels in relation to one-year survival were analyzed from the lowest value to the highest value and based on these results (see below), patients were categorized into three different BMI groups: BMI <22, 22-26, and ≥26. BMI <22 was used as a cut-off for underweight and risk of malnutrition as suggested by the Swedish National Board of Health and Welfare. The upper limit, BMI >26, was chosen after analysis of how various BMI levels relate to one-year survival. The middle group comprised patients with BMI 22-26, representing those between the lowest and highest cut-off values described above.

Follow-up study I

Patients were followed up at 12 months. Information on living condition was obtained by telephone interviews but also by using mailed questionnaires or by outpatient´s visits if needed because of reported problems from the hip. Mortality during the first year after the fracture was obtained from the hospital discharge register and the Swedish population records.

Study II

A total body BMD as well as a total hip BMD on the uninjured hip were obtained in the immediate postoperative period by DXA measurements. Height and weight were measured as described in study III and BMI was monitored. The biochemical parameters considered in study II were plasma-calcium (mmol/L), plasma-albumin (g/L) and serum-PTH (ng/L), which were analyzed according to standard hospital laboratory procedure for each center. Serum-25OHD (nmol/L) was analyzed at baseline and again after 12 months using chemiluminescence immunoassays (LIASON® 25OH vitamin D TOTAL Assay, DiaSorin Inc. Stillwater, MN, USA). To evaluate changes in bone turnover, serum-CTX-I (ng/L) was analyzed at baseline and at 12 months using the Beta-CrossLaps assay (Roche diagnostics GmbH, Mannheim, Germany), a 2-site immunometric (sandwich) assay based on electro-chemiluminescence detection. The interassay coefficient of variation (CV) was < 20%.

Study III

Fat mass (FM), lean mass (LM) and bone mineral content (BMC) were measured by DXA and expressed in kilograms (kg). Weight was calculated from the sum of LM, FM and BMC, obtained from the DXA measurements and defined as total body mass (kg); height was measured in supine position. ASA score, handgrip strength and HRQoL (EQ-5D) were assessed. Biochemical measures considered relevant to this study were analyzed. To serve as a nutritional biochemical marker, we analyzed serum levels of insulin-like growth factor-I (S-IGF-I, μg/L) by radioimmunoassay [75], and also used these levels to express an age-adjusted SD score; a score within 2 SD was considered within the age reference range [76, 77].

Follow-up studies II and III

In order to compare baseline results, DXA measurements of body composition, total hip and total body BMD were obtained at the 6 and 12 month follow-up visits, along with assessment of weight, handgrip strength and quality of life. Biochemical measurements were also analyzed at 6 and 12 months, except for serum CTX-I and serum 25OHD, which were analyzed only at the 12 month follow-up visit to compare with baseline.

Study IV

For this study we recorded age, sex, fracture type and number of comorbidities, as well as ASA and SPMSQ scores at inclusion. Surgical method, postoperative complications, and discharge to rehabilitation unit were also recorded. Due to the presence of dementia or severe cognitive impairment, information was obtained through proxy interviews with respect to living situation, ambulatory function, reliance on walking aids and ADL skills.

Follow-up study IV

Patients were followed up at 4 and 12 months regarding the above-mentioned variables. Information at the two follow-ups was primarily obtained by telephone interviews, as well as by mailed questionnaires or outpatient visits if necessary due to hip-related problems. In addition, information concerning healing complications, reoperation and mortality were obtained from hospital records. Ambulatory function at the two follow-ups was compared with ambulatory function on admission and if unchanged was referred to as “preserved” ambulatory function. Similarly, ADL index at the follow-ups was compared with ADL index on admission.

3.3 ASSESSMENT OF MOBILITY AND LIVING CONDITIONS

Ambulatory function was defined as: 1) ability to walk outdoors 2) ability to walk only indoors or 3) inability to walk.

Reliance on walking aid was defined as: 1) No aids or one cane; 2) walker or two canes; 3) wheelchair.

Patients admitted from their own home or service flats were defined as living independently and patients living in a nursing home or residential care facility were classified as institutionalized. Patient data also included whether they shared a household or lived alone.

3.4 DESCRIPTION OF INSTRUMENTAL ASSESSMENTS

American Society of Anesthesiologists (ASA)
A classification system used to assess a patient's physical status prior to anesthesia and surgery [73]. ASA 1 represents a completely healthy person, ASA 2 pertains to mild systemic disease, ASA 3 signifies a severe systemic disease that is incapacitating, ASA 4 reflects severe disease that is both incapacitating and a constant threat to life, while ASA 5 signifies a moribund person who is not expected to survive 24 hours with or without surgery. This grading system has been used as a comorbidity index and has been shown to predict mortality in hip fracture patients [78]. Patients scoring 3 or 4 are at higher risk of having complications compared with those in ASA class 2 [79].

In studies I and III patient were categorized as ASA 1-2 and ASA 3-4. In study IV patients were categorized as ASA 1-2, ASA 3 and ASA 4-5.

Activities of daily living (ADL)
The Katz ADL index describes the degree of independence/dependence in six basic activities of daily living (bathing, dressing, going to the toilet, transferring, continence, feeding) and was developed by Katz et al. [74]. ADL index A refers to independence in all six activities; B, dependence in one activity; C, dependence in bathing and one additional activity; D, dependence in bathing, dressing and one additional activity; E, dependence in bathing, dressing, going to the toilet and one additional activity; F, dependence in bathing, dressing, going to the toilet, transferring and one additional activity; G, dependence in all activities.

The Katz ADL index was used in studies I, III and IV. Patients were categorized into ADL index A-B or C-G.

Short Portable Mental Status Questionnaire (SPMSQ)

SPMSQ is a 10-item test, used to detect the presence of cognitive dysfunction and has shown good test-retest reliability [69]. It has been validated with similar rates of sensitivity and specificity to that of the Mini mental State Examination (MMSE), which is the most widely used screening test for the assessment of cognitive dysfunction [80, 81]. In comparison with the MMSE, the SPMSQ is easily administered to bedridden patients, as in the case of hip fracture, since it does not include writing exercises, which can be difficult to perform in supine position. Questions include orientation to time, place, memory, current event information and calculations. The number of errors are counted and low scores (0-2 correct answers) indicate severe cognitive impairment, 3-7 mild to moderate cognitive impairment, while 8 to 10 correct answers are considered as having intact cognitive function.

Only patients without severe cognitive impairment ($\geq$ 3 correct answers) were included in studies I, II and III. Study IV included patients with severe cognitive impairment (diagnosis of dementia and/or SPMSQ score of 0-2 points).

Health-related quality of life (HRQoL) according to EuroQol (EQ-5D)

EuroQoL is a standardized self-rating scale for health status containing five items (mobility, hygiene, activities, pain/discomfort and anxiety/depression), each with three levels of responses [82]; no problems, some problems or major problems. The items are compiled into a health index according to a mathematical formula [82]. An EQ-5D index of 0.00 indicate the worst possible health state and a value of 1.00 full health [82]. EQ-5D has been used to describe HRQoL in a general Swedish population [83], and has shown good responsiveness in elderly patients with femoral neck fractures [84].

The EQ-5D index was used in study III for assessment of health-related quality of life.

JAMAR hand dynamometer

Isometric muscle strength (kg) can be measured with a hand dynamometer. Hand grip strength (HGS) by the JAMAR dynamometer used in study III has previously shown good reproducibility (r >0.80) and reliability (r =0.98) [85, 86]. This measurement was performed with the patient sitting in a chair with a back support, forearms resting on the arms of the chair and wrists protruding just over the end. The highest value in the dominant hand from three tries was recorded [87]. Cut-off values used for low HGS were <30 kg in men and <20 kg in women [41].

Dual energy X-ray absorptiometry (DXA)

For clinical use, DXA provides the most accurate measure to calculate body composition including lean mass, fat mass and bone mineral content [15]. The DXA measurement is based on x-rays at two different energy levels. A detector measures the amount of energy absorbed or passing through the examined body part and is mathematically related to the density of tissues under measurement. Since the two energy levels are absorbed differently by soft tissue and bone, it is possible to distinguish between them. Radiation exposure is much lower than in chest x-ray [15] and measurement can be quickly performed.

Bone mineral density measured by DXA

BMD and body composition were measured using either Hologic (Hologic, Inc. Waltham, MA, USA) or GE Lunar (Madison, WI, USA) densitometers. The DXA image is two-dimensional and BMD was expressed as areal density, grams per square centimeter (g/cm²), and as standard deviation in relation to both mean value among healthy young individuals (T-score) and mean value of age-and sex-matched adults (Z score). To compensate for variation in BMD measurements among different centers and densitometers, equations to standardize bone mineral density were used to create sBMD in mg/cm² for the total hip results [88]. To calculate changes in BMD, the areal BMD (g/cm²) was used [13]. Since patient position is important when comparing repeated total hip measurements, a device to stabilize leg rotation was used. Baseline and follow-up images were compared regarding region of interest (ROI). The precision error (GE Lunar) of the BMD results was tested on 30 outpatients on two occasions according to International Society for Clinical Densitometry (ISCD) guidelines [89] and showed 0.010 g/cm² for the total hip and 0.007 g/cm² total body BMD, respectively.

Body composition measured by DXA

DXA measurements of body composition represent a 3-compartment model that includes fat mass (FM), bone mineral content (BMC) and lean mass (LM). Lean mass is composed of muscle, visceral organs and water. The sum of LM and BMC represents fat-free mass (FFM). To normalize for body size, FFM and FM were divided by height squared to calculate fat-free mass index (FFMI, kg/m²) and fat mass index (FMI, kg/m²) [90]. Cut-offs for low FFMI were <17 kg/m² for men and <15 kg/m² for women [91], based on reference values for body composition in a Swiss population [91]. Thus, a FFMI lower than the 10th percentile of the reference population was considered to be low [91, 90]. Data on lean mass from DXA measurements of legs and arms were used to calculate appendicular skeletal muscle mass (kg) [92]. The lean mass of the un-fractured leg multiplied by 2 was used at baseline to avoid overestimation in the fractured leg due to postoperative edema [47]. An appendicular lean mass index (aLM, kg/m²) was calculated by dividing appendicular lean mass (aLM, kg) by height squared [92]. Cut-off points used for low aLMI were ≤7.23 kg/m² for men and ≤5.67 kg/m² for women [93]. Reproducibility has been reported to be good for whole body DXA, LM ($r = 0.99$)

and FM (r =1.00) [94]. Among several factors, reproducibility depends on accurate positioning of the patient [94]. Hydration status when calculating fat-free mass is another potential source of error [15].

3.5 STATISTICS

IBM SPSS version 22.0 was the statistical software used in studies I, II and III; version 16.0 for Windows (IBM, SPSS Statistics) was used for study IV. Mean, standard deviation, median, range and percentage were used in all four studies for descriptive purposes. The Student's t-test was used to test for differences in normally distributed independent variables and the Kruskal-Wallis test was used to compare variables not normally distributed. In studies I and IV contingency tables were tested for differences using the Chi-square test. Fisher's exact test was used for contingency tables when cells counts were expected to be less than 5. A p-value of < 0.05 was considered significant.

Study I

One-way analysis of variance (ANOVA) was used to test differences between groups regarding age. The association between the three BMI groups and one-year survival was evaluated using binary logistic regression analyses, both unadjusted and adjusted for age, sex and ASA score. The association between BMI groups and capacity for independent living following hip fracture were similarly analyzed and adjusted for age, sex, ASA score and shared household upon admission.

Studies II and III

Normal distribution of serum-CTX-I was achieved through transformation using a logarithmic scale. A paired samples t-test was used to compare intra-group differences in serum-CTX-I between baseline and 12-month follow-up. Non-parametric tests were used to analyze EQ-5D data. Univariate correlations between FFMI and aLMI, and between aLMI and HGS were analyzed using Pearson correlation coefficient and Spearman´s rank correlation coefficient, respectively. Differences between the three treatment groups were analyzed using covariance of analysis (ANCOVA). The ANCOVA analyses included exposure measures, treatment groups and sex as fixed factors. Age and baseline values for BMD, FFMI, FMI, serum-CTX-I, serum-25OHD and HGS were included as covariates. Baseline value was the only covariate used in the analysis of serum-PTH. Data were reported using complete-cases analysis and intention-to-treat (ITT) analysis. Missing data were processed for each of the outcome measures according to the hot-deck method [95], which replaces missing data with randomly assigned values taken from individuals stratified according to sex and age. ITT analyses were performed using the database with imputed data.

Sample size in study II and III was based on lean mass.

Study IV

In order to investigate associations with outcome pertaining to ambulatory function, ADL index and discharge to a rehabilitation facility, the following factors were included in a stepwise logistic regression analysis: age, sex, ASA score, number of comorbidities, ambulatory function before fracture, ADL index before fracture, type of fracture, surgical method, discharge to rehabilitation unit, living situation, major complications and reoperation.

3.6 ETHICS

Ethical considerations arise when data are collected on patients unable to provide consent due to cognitive impairment. Another ethical dilemma involves inclusion of frail patients in a vulnerable situation, such as after a hip fracture, which entails performing various measurements that may cause discomfort. However, inclusion of these frail patients in studies is of great importance for improving care and outcome. Patient discomfort must be weighed against the benefits of new knowledge and potential improvements in treatment. Another issue of concern in study II was that some patients who were defined as having osteoporosis were randomized to treatment with calcium and vitamin D alone, which is not evidence-based treatment for osteoporosis. However, at the time this study was carried out, calcium and vitamin D were regarded as basic treatment and patients with osteoporosis were offered follow-up in primary care after study completion.

All studies were approved by the local ethics committee and were performed in accordance with the Helsinki Declaration [96]. Participants provided written consent to participate in the studies. In patients with severe cognitive impairment written consent was obtained from a close relative or caregiver.

4 RESULTS

4.1 STUDY I

The average age of all study participants was 82 years (SD 7); 73% were women and mean BMI was 22.7 kg/m². Of 843 patients, 128 (15%) died during the first year after fracture. Mortality rate among men was 19% and among women 14% (p=0.06). The three BMI groups differed by age and sex, but not regarding fracture type, ASA score, ADL index, proportion living alone or reliance on walking aids. Mortality rates for those with a BMI of <22 and 22-26 were 16% and18%, respectively, while the corresponding figure for those with BMI >26 kg/m² was 6%. Both age and ASA score were found to be independently associated with one-year mortality, while sex was not. Logistic regression analysis showed BMI to be independently related to one-year survival; odds ratio (OR) for the group with BMI >26 kg/m² was 2.58 (CI 95%; 1.22-5.46), p=0.01 after adjustment for age, sex and ASA score.

A total of 25% had not returned to independent living one year post-hip fracture. Remaining at institution were 28% of the patients with BMI <22 and 27% of the patients with BMI 22-26, whereas the corresponding figure for patients with BMI >26 was 12%, (p=0.003). Significant factors related to independent living were age, ASA score and shared household, but not sex. Patients with BMI >26 were more likely to return to independent living 12 months post-hip fracture; OR 2.62 (CI 95%; 1.37-5.02), p <0.01 after adjustment for age, sex, ASA score and shared household upon admission. There were no differences regarding mortality or independent living one year post-fracture among patients with BMI <22 kg/m² (cut-off for underweight in older adults), p=0.6, and among those with BMI 22-26 kg/m², p=0.95.

4.2 STUDY II

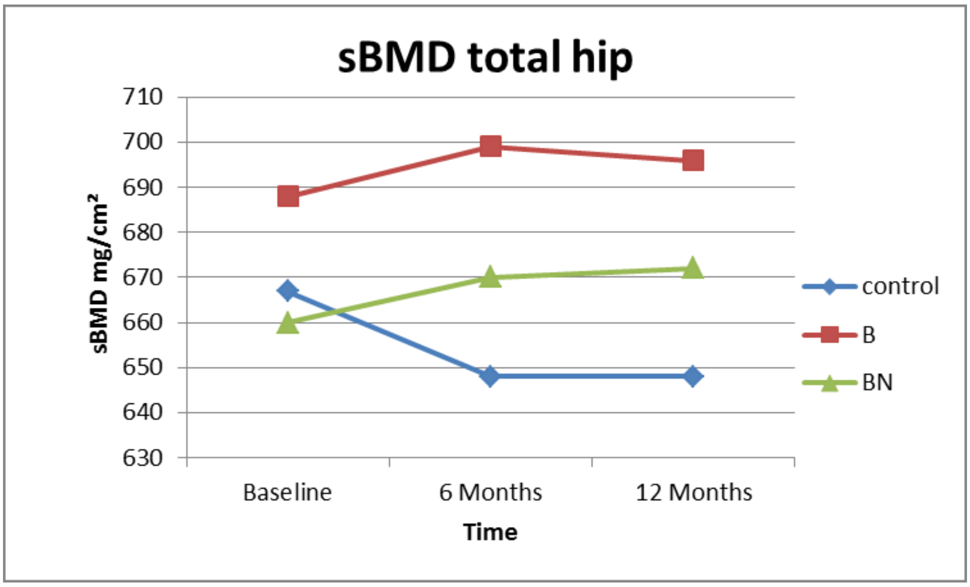
Seventy-nine patients were initially included in the study, of whom 67 were available at final follow-up. All patients were measured by DXA at inclusion; 68 were measured at 6 months and 66 at12 months. Because 9 patients had a total hip replacement on the uninjured side, their hip measurements could not be taken. The mean age of all included patients was 79 years (SD 9); 56 (71%) were women. Other than reliance on walking aids, there were no significant differences between the three treatment groups. Complete-case analysis showed an increase in total hip BMD of 0.7% in the nutritional supplementation group (BN), whereas the bisphosphonate (B) and control (C) groups lost 1.1% and 2.4% of BMD, respectively, between baseline and 6 months (p=0.071). Standardized BMD (sBMD) at the total hip in absolute values (mg/cm²) at baseline and at follow-up are displayed in the figure below (Figure 3).

There was no change in total body BMD between baseline and 12 months in the BN group, while the B group and C group both lost BMD, C more so than B (p=0.009). The findings from the intention-to-treat analysis (ITT) were in line with the complete-case analyses, showing significant group differences in total hip BMD at 6-month follow-up (p=0.03) and in total body BMD at 12-month follow-up (p=0.03).

There was a trend toward differences in serum CTX-I after 12 months (p=0.055) that was confirmed by the intention-to treat analysis, which showed a more pronounced decrease within the B and BN group compared with the C group (p=0.019). An analysis of intra-group changes in serum CTX-I between baseline and 12 months showed a significant decrease in the BN and B groups of 36% and 33%, respectively (p <0.001), whereas the C group showed a smaller, non-significant decrease of 12% (p=0.77).

A total of 59% (n=47) of all participants had a baseline serum-25OHD below normal (< 50 nmol/L); 11 of them had values indicating severe deficiency (< 25 nmol/L). At the12-month follow-up 26% of patients still had serum-25OHD concentrations < 50 nmol/L. Average serum-PTH was within normal range for all groups at inclusion and remained normal during follow-ups. There were no significant differences between the three treatment groups in serum-25OHD or serum-PTH on any measurement occasion; this result was supported by the ITT analyses.

Figure 3 Standardized BMD (sBMD) at the total hip in absolute values (mg/cm²) at baseline and at follow-up



Abbreviations: sBMD, standardized bone mineral density; BN: bisphosphonate together with nutritional supplementation and calcium + vitamin D; B: bisphosphonate and calcium + vitamin D; C: controls treated with calcium + vitamin D

4.3 STUDY III

The study population for this study was the same as for study II. Baseline measurements showed low FFMI in 22 of 79 (28%) patients and low aLMI in 32 of 79 (40%). A strong positive correlation between FFMI and aLMI was found, r=0.92, p <0.01. The total number of patients defined as having sarcopenia (both low aLMI and low HGS), was 16 out of 75 (21%) at baseline; the corresponding figures at 6 and 12 months were 24% and 29%, respectively, with no significant difference between groups over the observation period. During the first year an overall loss of body mass and FFM were found. Complete-case analyses showed a trend toward increased FMI with a pronounced decrease in FFMI and aLMI in the N group, shown in the table below. The ITT analyses confirmed this trend, showing no loss in FMI at 6 months (p=0.01) and a greater loss of FFMI in the N group compared with the other two groups at 6 and 12 months (p <0.001 and p=0.006, respectively). A moderate positive correlation was found between aLMI and HGS at baseline (rs=0.47, p <0.01), and at 6 (rs=0.61, p <0.01) and 12 months (rs=0.64, p <0.01)

Table 1 Outcome of body composition components in study III

		All patients	Group N	Group B	Group C	
	Months					p-value
Body mass, kg (SD), %	[a]0-6 [b]0-12	-2.1 (3.5), -3.4 -1.6 (4.0), -2.8	-2.0 (3.5), -3.7 -1.8 (3.0), -3.2	-3.0 (3.8), -4.3 -2.2 (4.6), -3.0	-1.2 (3.2) -2.3 -0.9 (4.1) -2.1	0.29 0.69
FFM, kg (SD), %	[a]0-6 [b]0-12	-1.5 (2.5), -3.3 -1.6 (2.7), -3.5	-2.4 (2.0), -5.5 -2.2 (2.5), -5.1	-1.3 (3.2), -2.6 -1.4 (3.2), -2.9	-1.0 (1.9), -2.4 -1.3 (2.2), -2.9	0.09 0.41
FM, Kg (SD), %	[a]0-6 [b]0-12	-0.6 (2.9), -2.7 -0.2 (3.4), -0.2	+0.4 (2.3), +1.0 +0.4 (2.1), +3.1	-1.7 (3.6), -7.0 -0.7 (4.4), -0.9	-0.2 (2.1), -1.2 -0.1 (3.0), -1.9	0.06 0.64
aLM, kg (SD), %	[a]0-6 [b]0-12	-0.1 (1.6), -0.3 -0.2 (1.6), -1.5	-0.7 (1.4), -3.9 -0.4 (1.5), -3.1	+ 0.3 (1.9), +1.8 -0.02 (2.0), -0.6	+0.02 (1.4), +0.3 -0.2 (1.4), -1.2	0.06 0.40
FFMI, kg/m² (SD), %	[a]0-6 [b]0-12	-0.6 (0.9), -3.3 -0.6 (1.0), -3.5	-0.9 (0.7), -5.5 -0.8 (0.9), -5.1	-0.4 (1.2), -2.6 -0.5 (1.2), -2.9	-0.4 (0.8) -2.4 -0.5 (0.8) -2.9	0.08 0.31
FMI kg/m² (SD), %	[a]0-6 [b]0-12	-0.2 (1.1), -2.7 -0.1 (1.2), -0.2	0.1 (0.8), +1.0 0.1 (0.8), +3.1	-0.6 (1.4), -7.0 -0.3 (1.6), -0.9	-0.1 (0.8) -1.2 -0.1 (1.1) -1.9	0.06 0.62
aLMI kg/m² (SD), %	[a]0-6 [b]0-12	0.0 (0.6), -0.3 -0.1 (0.6), -1.5	-0.2 (0.5), -3.9 -0.2 (0.5), -3.1	+0.1 (0.7), +1.8 0.0 (0.7), -0.6	0.0 (0.6), +0.3 -0.1 (0.5), -1.2	0.03 0.30

Abbreviations: FFM, Fat Free Mass; FM, Fat Mass; aLM, appendicular Lean Mass; FFMI, Fat Free Mass Index; FMI, Fat Mass Index; aLMI, appendicular Lean Mass Index

Complete-cases analyses showed a trend toward improved HGS in the N group, although this was not confirmed by ITT analysis. Intra-group analyses showed a significant increase in HGS within the N group between baseline and 6 months (p=0.04), but this change was not significant in the other two groups. The EQ-5D index decreased from 0.86 (SD 0.22) at baseline to 0.79 (SD 0.21) at 6 months and 0.74 (SD 0.24) at 12 months for all patients, but no difference was found between groups at either of the two follow-ups, p=0.57 and p=0.50, respectively. Intra-group analysis showed a significant decrease in the EQ-5D index during the first year for the C and B groups (p=0.03 and p=0.01, respectively), but not for the N group (p=0.22). Average levels of S-IGF-I and age-adjusted SD score were within normal range in all groups at baseline and showed no differences between groups on any measurement occasion. The increase in S-IGF-I found in all groups between baseline and 6 months did not differ among them (p=0.39).

4.4 STUDY IV

One hundred of the included patients were living independently on admission and 70% of them were discharged to rehabilitation facilities after surgery, while the corresponding figure for patients admitted from institutions was 8%. At the 4-month follow-up, 62% were still ambulatory, as were 57% at 12 months. Patients who were discharged to rehabilitation facilities were more likely to remain ambulatory at both time points; odds ratio (OR) 2.84 (CI 95%; 1.16-6.90), p=0.02 at 4-months and OR 2.83 (CI 95%; 1.10-7.26), p= 0.03 at 12-months. Ambulatory function prior to fracture was also associated with preservation of ambulatory function on both measurement occasions, while surgical method was not. At the 4-month follow up, 22% of patients were wheelchair-bound and the corresponding figure for the 12-month follow-up was 28%. Discharge to rehabilitation facilities was associated with decreased risk of becoming wheelchair-bound; OR 0.26 (CI 95%; 0.08-0.83), p=0.02 at 4-months. At the 4-month follow-up, major complications, major reoperations and age were also significantly associated with being wheelchair-bound, while type of surgical method was not (p=0.67). Independent factors related to wheelchair dependence at 12 months included only discharge to rehabilitation facilities and major complications.

At the 4-and 12-month follow-ups, 57% and 48% respectively had preserved ADL skills. When adjusted for age and sex, the results showed that patients who were discharged to rehabilitation facilities were more likely to have preserved ADL skills; OR 4.24 (CI 95%; 1.61-11.17), p=0.02 at 4 months and OR 5.33 (CI 95%, 1.44-19.65), p=0.01 at 12 months. ADL index prior to fracture was also a significant factor for preserved ADL skills.

5 DISCUSSION

The first overall theme of this thesis was to describe the significance of body mass index for survival and independent living one year after hip fracture. The second theme was to evaluate whether efforts to promote nutrition could benefit BMD, bodyweight, lean mass, strength and thereby health-related quality of life. The third theme was to describe potentially modifiable factors of importance to regain walking ability and ADL function after hip fracture.

5.1 STUDY I

In this group of hip fracture patients, overweight and obesity were associated with lower risk of death and a higher rate of independent living one year post-fracture. Among geriatric patients in general, the mortality rate has been considered to be higher in those with underweight (defined as BMI ≤20 [97] and BMI <22 [98]) than in those with normal and high BMI (>25 kg/m²) [99]. In line with this assumption, the present study showed a higher one-year mortality rate not only among patients with BMI <22, but also among those with BMI 22-26, compared with patients with BMI >26. This finding in hip fracture patients has not been presented previously, although earlier studies have shown that patients with a BMI ≤20, as well as those with a BMI in the lowest quartile, have been reported to be at increased risk for mortality [71, 100, 23]. Consistent with our findings, a recent study on fracture patients in general, aged ≥40 years, showed a reduced risk of death among overweight (BMI 25-29.9 kg/m²) and obese (≥30 kg/m²) individuals compared with those of normal weight (18.5 to < 25 kg/m²)[101]. Similarly, an increased mortality rate has been shown in patients with BMI ≤24 undergoing cardiac valvular surgery [102], as well as a lower risk of death in obese patients following primary shoulder arthroplasty [103]. A lower risk of mortality among individuals with BMI up to 30 kg/m² has also been reported in a cohort study of patients with dementia [104]. These observations have been termed “the obesity paradox” indicating that among the elderly, obesity is inversely associated with a lower, not higher, risk of death [105]. Obesity as a risk factor for cardiovascular disease and increased mortality is otherwise a well-established paradigm in the adult population at large [106, 107]. Among the suggested explanations for “the obesity paradox” in the elderly are competing risk factors, comorbidities and survival bias. Another suggested explanation is that obesity in the elderly may have a protective effect against oxidative stress and inflammation [108, 109]; however the underlying mechanisms remain unclear. The findings in the present study may imply that a larger energy reserve is needed to meet the increased metabolic demands associated with trauma and postoperative catabolism following hip fracture and surgical procedures in general [110,111].

The age and sex distribution in the present study corresponded well to previous reports concerning hip fracture patients, which makes our study population representative [112, 113]. A significant number of patients had low BMI, indicating risk of malnutrition, which is in line with earlier reports on patients with hip fracture [23, 24, 114]. The results in the present study showed a lower overall one-year mortality of 15% compared with previous studies showing 22-29% [115,116]. One possible explanation for this finding was the exclusion of patients with severe cognitive impairment and those living in nursing homes. These factors are well known to be associated with an increased mortality rate [11, 117, 118].

Advanced age, sex, comorbidities prior to fracture, pre-fracture level of function, history of dementia and living situation (alone or with others) are all factors reported to influence the ability to return to independent living following hip fracture [119]. In contrast to the current study, no prior study has shown that overweight and obesity are associated with a higher probability of independent living 12 months after a hip fracture. On the other hand, both low BMI and weight loss after hip fracture have been associated with weakness and poor function in regard to walking speed at 6 months and handgrip strength at 12 months postoperatively [120]. One earlier report on geriatric patients in general has also shown low BMI and underweight to be risk factors for functional decline [121]. Furthermore, low BMI in non-disabled but medically ill patients at the time of hospital admission has been reported to predict impaired ADL function at the time of discharge [122], thereby likely affecting the ability to live independently.

Strengths and limitations study I

BMI was only assessed at inclusion and weight change over time was not recorded, so the only conclusion that could be drawn is that BMI at time of fracture was associated with outcome after one year. However, earlier studies have shown that weight loss is common following hip fracture [123, 120, 124]. Furthermore, weight loss along with loss of total lean mass and loss of fat mass have been associated with increased mortality among men 65 years or older [125]. Another limitation is that BMI does not provide detailed information on body composition, neither on the distribution nor on the ratio between lean and fat mass.

The prospective design with a large number of consecutively enrolled patients was a major strength of this study, while the focus on studying a group of relatively healthy elderly hip fracture patients added novelty.

5.2 STUDY II

We found that nutritional supplementation in addition to calcium, vitamin D, and risedronate had a beneficial effect on total hip BMD and total body BMD in elderly patients with a recent hip fracture. An annual loss of 0.27% and 0.25% of total hip BMD in women and men, respectively, has been reported for a healthy population, aged 50-85 years [126], but a higher protein intake in elderly individuals has been associated with lower bone loss [127] and higher bone mineral content [128]. Conflicting with these findings is the hypothesis that high protein intake results in increased bone loss due to higher acid load [129]. According to this line of thinking, high acid load needs to be buffered, which leads to release of calcium together with carbonate from the skeletal reservoir through increased osteoclast activity, thereby causing increased bone loss [129]. Yet it has also been reported that increased urinary excretion of calcium due to high protein intake had no deleterious effects on calcium retention [130]. Further results from the same study showed an increase of IGF-I, which is generally assumed to have anabolic effects on bone mass [130]. The thinking underlying the present study was to compensate an assumed poor intake of protein and the hypothesis was that this would reduce loss of bone mass following hip fracture. A trend toward an increase in total hip BMD after 12 months on a protein-containing supplement has been observed, along with a decrease in serum CTX-I, in a study of 71 community-dwelling women with low BMI ($\leq$21 kg/m²) [131]. Earlier studies have shown a loss of 2.0-4.6% of BMD in the uninjured hip during the first year following hip fracture [39, 40,] which is consistent with the findings in the control group for the current study.

A lower incidence of a second hip fracture has been reported in patients treated with risedronate [132]. Previous studies have also reported an increase in total hip BMD post-hip fracture following treatment with parenterally administered bisphosphonate [63, 133]. The present study involved oral administration of bisphosphonate, which could explain the lower net gain in BMD compared with the previous study [63], since absorption of orally administered treatment is low even under ideal circumstances. Another important consideration is the well-known suboptimal patient compliance with orally administered bisphosphonates [134, 135], which we also observed in the current study.

A few previous studies have explored the possible effects of protein and energy-rich nutritional supplements on BMD following hip fracture. A randomized trial of 60 women with hip fracture evaluated the treatment effects of protein-rich supplementation alone or in combination with anabolic steroids on both hip and total body BMD [136]. Although the difference in BMD between the groups did not reach statistical significance, the results of that study indicated an increase in total body BMD at 6 and 12 months in the groups that received protein and energy supplementation, compared with the group treated with calcium and vitamin D alone [136]. Yet another study of 82 hip fracture patients showed that protein supplementation (20 grams daily) for 12 months following hip fracture preserved BMD, compared with untreated controls [51]. The nutritional supplementation used in our current study provided a 40 g daily dose of protein, compared with only 20 g in the previous studies [51, 136], which may explain the BMD-preserving effect observed after only six months. Furthermore, participants in our study received 600 kcal/day in supplementation, instead of the 250 kcal/day in one of the previous studies [51]. Unlike previous studies, patients in the current study were also treated with drugs that inhibit bone resorption [51, 136]. The mean change in total hip BMD in the present study did not reach statistical significance, but the explanation may lie in the small group sizes. However, the intention-to-treat analysis supported the results of complete-case analysis, showing a significant difference between groups in total hip BMD at 6 months and total body BMD at 12 months.

We found no differences in vitamin D levels between groups to explain the disparities in BMD. All patients received vitamin D and the mean values of serum-25OHD were normalized in each group during the study period. However, 26% of all included patients still had values < 50 nmol/L at the final follow-up, which is consistent with the results from a prior study in which hospitalized women aged 66 to 95 were treated with vitamin D3 (800 IE) and calcium (1000 mg) [137]. Possible explanations for why all patients did not normalize their 25OHD concentration include insufficient vitamin D dose, a short 3-month period of supplementation and noncompliance issues [137]. The first and last of these reasons may also apply to the current study.

The decrease in bone resorption marker S-CTX-I levels became more pronounced in both risedronate-treated groups at 12 months. Since bone resorption inhibitors decrease CTX levels, these results reflect the expected treatment response to risedronate. An earlier study concerning the natural course of bone resorption markers following fracture showed an increase in the levels within two weeks and the levels remained elevated for up to a year compared with pre-fracture levels [36]. CTX levels vary greatly among individuals. The degree of increase post-fracture depends on the size of the fractured bone, but other causes of variability include circadian rhythm, food intake and physical activity - factors that the present study did not take into account [34, 37].

Strengths and limitations study II

The selection of slightly younger and healthier than average hip fracture patients makes it impossible to generalize the results. Group size was also a limiting factor, as was lack of compliance despite regular telephone follow-ups. Although the study lasted for one year, the nutritional supplementation was only provided during the first 6 postoperative months, when the degree of catabolism is likely to be most pronounced.

The combined treatment with bisphosphonate and nutritional supplementation was novel and the randomized design was one of the strengths, as was the relatively long treatment period.

5.3 STUDY III

In this study we found that nutritional supplementation in addition to bisphosphonate, calcium and vitamin D produced no additive effect on lean mass, handgrip strength or HRQoL compared with either bisphosphonate with calcium and vitamin D, or calcium and vitamin D alone. Thus, none of the study hypotheses could be confirmed. The results of the intention-to-treat analysis were in line with those of the complete-case analysis. However, intra-group analysis did show a beneficial effect on HRQoL, as well as improved HGS in the nutritional supplementation group. These intra-group differences may indicate that the study was underpowered and therefore unable to answer the questions posed. Post-hoc analyses showed that at least 135 patients (vs the 79 in this study) would be needed to reach statistical significance between groups to address effect on HGS. Furthermore, because some studies suggest that vitamin D has beneficial effects on muscle strength, the administration of vitamin D to all groups may have negated any significant differences in treatment effects among groups [138, 139]. However, other studies have failed to show any effect of vitamin D on muscle strength [140, 141]. The finding of lean mass loss despite protein-rich nutritional supplementation following hip fracture is consistent with a previous study [142]. Loss of lean mass in the prior study was 1.6 kg (SD 1.5) and in the present study 2.1 kg (SD 2.6) during the first year post-fracture, despite nutritional supplementation in both studies. The prior study showed that lean mass was preserved during the first 6 months only among patients who received an anabolic steroid in addition to supplementation [142]. Loss of lean mass following hip fracture has been reported at 5-6 % during the first year [123, 39, 40], which is in line with the observed loss of 5.2% in our study, even though our patients received nutritional support for 6 months.

A negative energy balance in response to injury possibly explains the difficulties in benefitting from nutritional supplementation, since the metabolic, hormonal and inflammatory response to trauma and surgery results in an accelerated and prolonged breakdown of muscle protein [111, 143]. Moreover, it is important to keep in mind that many hip fracture patients suffer from poor nutrition [144] and a negative energy balance already prior to hip fracture [123, 145]. Recently, focus on the composition of protein supplementation has increased as indications have emerged that certain essential amino acids, specifically the branched-chain amino acid leucine that is abundant in whey protein and its metabolite hydroxy-methyl-butyrate (HMB), may have anabolic effects in addition to purely nutritional effects [146,147]. The current study used a traditional balanced mix of proteins. Further studies are needed to assess whether more explicit beneficial effects could be obtained using these specific protein compounds.

The proportion of patients with sarcopenia did not differ among groups over the observation period. The prevalence of sarcopenia was 21% at baseline, and 24% and 29%, respectively after 6 and 12 months, which confirms earlier reports of a catabolic state that persists during the first year post-hip fracture [33]. The proportion of hip fracture patients with low aLMI at baseline has previously been reported to be 47%, compared with 40% in the present study [48]. This slight difference may be due to differences in the selection of patients as well as to the use of different normative data. We found a higher proportion of patients with low aLMI at both 6 and 12 months than at baseline, but no previous studies with aLMI results up to one year following hip fracture are available for comparison. A trend toward preserved FMI was seen at 6 months in the nutritional supplementation group, which was strongly supported by the intention-to-treat analysis; similar effects on FMI were shown in a previous study using nutritional support prior to elective hip surgery [148]. A possible explanation for preserved FMI, albeit not FFMI, through nutritional supplementation in the present study might be the effect that the lack of resistance training during rehabilitation could have on fat metabolism. However, exercise programs with resistance training combined with nutritional supplementation have been reported to result in gain of both lean mass and fat mass [149].

We found improvement in HGS within the protein and energy supplementation group between baseline and 6 months. A similar improvement in HGS after 3 months of nutritional supplementation has been shown earlier in elderly patients following hospitalization due to acute illness, as well as in chronically-ill outpatients [150,151]. This is important, since sarcopenia is not defined by reduced muscle mass alone, but by the combination of reduced muscle mass and reduced muscle strength or physical performance [41]. The reason for this is that function, as indicated by strength and/or physical performance, is a complex parameter that relates to more than just muscle mass, and that muscle function may improve, even when muscle mass remains unaffected [152, 153, 154]. This may help explain our findings in the nutritional supplementation group that show a trend toward preserved HGS, but not FFMI, as well as the modest relationship between HGS and aLMI found in our analysis. We chose to study HGS in the present study since a strong association has been shown between HGS and leg muscle strength, and also because HGS actually predicts mobility better than muscle mass [49, 155]. Consistent with these earlier reports on HGS, recent studies showed HGS but not appendicular lean mass to be independently associated with functional outcome after hip fracture [154, 156].

HRQoL decreased in all groups and failed to reach pre-fracture levels by 12 months, findings consistent with an earlier study following hip fracture [157]. However, intra-group analysis showed less decline in the nutritional supplementation group. Preservation of HRQoL after hip fracture has not previously been seen following supplementation alone, but has been demonstrated when supplementation was combined with an anabolic steroid [142].

Strengths and limitations study III

As mentioned above, one major limitation is the small number of study subjects, which may lead to type 2 errors, i.e. the risk of missing a true positive effect. The difficulties of including large numbers of hip fracture patients in intervention studies with nutritional supplementation are generally acknowledged [54]. Other limitations include the high attrition rate and suboptimal compliance in the nutritional supplementation group, both of which have been encountered in earlier studies [158, 159]. Further, intervention was first initiated postoperatively, which may have reduced the ability to counter the effects of the catabolic process already underway before surgery. Another limitation was that due to the multicenter design of the study, patients were examined by different DXA systems. However, patients were randomized to all treatment groups and were measured by the same DXA equipment at all three occasions.

The strength and novelty of this study lie in the DXA measurements of body composition, with assessment of changes in fat-free mass, fat mass, appendicular muscle mass, strength and HRQoL, for evaluation of the response to oral nutritional supplementation following hip fracture in the elderly. Other attributes include assessment of appendicular lean mass index together with HGS to determine the prevalence of sarcopenia in the study population not just at baseline, but also postoperatively for one year.

5.4 STUDY IV

This study showed that discharge to rehabilitation was associated with preserved ambulatory function, ADL skills and less risk of becoming wheelchair-bound in patients with femoral neck fracture and cognitive impairment. As shown in previous studies, pre-fracture function was also associated with preserved ambulatory and ADL function following fracture [160, 161].

Rehabilitation is crucial for regaining pre-fracture ambulatory and ADL function following hip fracture [66, 162]. A multidisciplinary rehabilitation program has been shown to reduce the risk of falls, even for patients with dementia [163]. Furthermore, previous studies have shown that patients with cognitive impairment can regain pre-fracture mobility and ADL function if they undergo targeted rehabilitation following hip fracture surgery [72, 164, 165, 166]. One study reported that pre-fracture mobility rather than cognitive level is associated with regaining motor function after hip fracture [160]. Others have shown that the association between cognitive impairment and poor functional outcome in patients with hip fracture was actually dependent on rehabilitation participation [167, 168], yet patients with dementia are less likely to be admitted to rehabilitation facilities [169].

In the present study, the strongest factor for discharge to rehabilitation was patient's previous living situation, also consistent with a previous report [170]. As in other studies, we found that patients who were admitted to a hospital from an institution were seldom considered for inpatient rehabilitation after discharge from an acute care hospital [171]. In general, patients admitted from institutions have shorter hospital stays and are discharged from the acute care hospital as soon as they are medically stable [172]. Possible explanations may be the perception that these patients fare better in a familiar environment, or that community-based nursing homes offer adequate rehabilitation resources, for which reason their patients are not considered for rehabilitation in outside facilities. However, the situation may also reflect an attempt to increase efficiency [173] or a shortage of beds in geriatric rehabilitation facilities. Since it is likely that patients admitted from residential care homes are more frail than those living independently [118], they may benefit from the support of a rehabilitation team to cope with their new situation following hip fracture. Nevertheless, it may be reasonable to assume that there is a general shortage of rehabilitation resources in community-based nursing homes. In line with our findings a prior study showed that those discharged to rehabilitation facilities had superior function at 12 and 24 weeks compared with patients in nursing homes, even after controlling for important confounders [174, 170].

The present study also showed that about one third of all patients were wheelchair-bound at the 12 month follow-up, which is consistent with a previous study [175], but we found that patients who were discharged to a rehabilitation facility were less likely to become wheelchair-bound. Reoperation was also associated with wheelchair use, but only at the 4-month follow-up.

Since our study was published, other researchers have obtained similar results that strengthen our findings. For example, one study has reported that even patients with moderate to severe cognitive impairment can achieve independent ambulation after hip fracture rehabilitation, a result that was maintained at one year [176]. Another recently published study which also corroborated our findings showed that pre-fracture motor function, but not cognitive impairment (SPMSQ < 3), was associated with preserved ambulatory function and pre-fracture ADL skills 4 months after fracture [177].

Strengths and limitations study IV

Due to selection of patients with cognitive impairment, all data were collected by proxy interviews. No reliability testing of information provided by proxy was undertaken in the present study, but previous studies have shown that proxy-patient agreement is reasonably accurate for concrete observable variables and moderately reliable for subjective variables [178, 179]. No information relevant to decisions concerning discharge to rehabilitation facilities was collected. However, patients discharged to rehabilitation facilities were found to be similar to those who were not regarding cognitive function, age, gender, ASA score, fracture type, surgical method and ambulatory function prior to fracture. Since cognitive impairment may be a manifestation of both dementia and delirium, one methodological issue to be acknowledged is that the SPMSQ in the current study made no distinction between these two conditions. However, an SPMSQ score of <3 was defined as severe cognitive impairment for the purpose of the current study and is known to be associated with poor outcome regarding ambulatory function, ADL skills and mortality post-hip fracture, irrespective of whether the diagnosis is delirium or dementia [11, 12, 180].

The choice of ambulatory function and ADL skills as primary outcome variables was a strength of the study since these variables are important for autonomy and health-related quality of life [45]. Another strength of our study was the rather low attrition rate.

6 CONCLUSIONS

Overweight and obese patients achieved a better one-year survival rate and were more likely to return to independent living than patients with normal or low weight. The addition of protein and energy-rich supplementation to orally administered bisphosphonate showed a small additive effect on total hip and total body BMD postoperatively in the group of hip fracture patients receiving this treatment. However, nutritional supplementation combined with conventional rehabilitation did not preserve fat-free mass any better than taking vitamin D and calcium alone, or together with bisphosphonate. There were no inter-group differences concerning effects on HGS or HRQoL, but intra-group analysis indicated beneficial effects on both these outcomes. The study on hip fracture patients with cognitive impairment showed that, ambulatory and ADL function prior to hip fracture and discharge to a rehabilitation facility were independently associated with preserved ambulatory and ADL function 4 and 12 months postoperatively.

The findings in the studies, indicate that elderly hip fracture patients may benefit from being overweight; however, the underlying mechanisms are unclear and further research is needed. Because the aging process itself is associated with decreasing physiological reserves, a low BMI on hospital admission may already signal a marginal nutritional status. The findings of the association between BMI and both one-year survival and capacity for independent living are of importance since body weight is a potentially modifiable factor. The interventional study indicates minor beneficial effects on BMD, FM, HGS and HRQoL; further research is needed to verify these effects and whether good nutritional status may reduce morbidity, mortality and risk of fracture following hip fracture. In the meantime, it would seem reasonable to prevent postoperative weight loss, for which reason recommendations for optimal BMI need further consideration in this patient group. Lastly, in order for patients with hip fracture and cognitive impairment to achieve better functional outcome, it is likely important to provide access to rehabilitation.

7 POPULÄRVETENSKAPLIG SAMMANFATTNING

Höftfraktur är ett samlingsnamn för benbrott i övre delen av lårbenet. Bakomliggande riskfaktorer för höftfraktur är flera men en av de starkaste är benskörhet s.k. osteoporos som kännetecknas av låg bentäthet och ökad risk för benbrott. I Sverige inträffar ca 70 000 osteoporosrelaterade benbrott varje år varav 18 000 utgörs av höftfrakturer. Medelåldern hos de som drabbas av höftfraktur är 82 år och 68 % är kvinnor. Hos personer över 70 år uppkommer de flesta höftfrakturerna inomhus genom fall i samma plan. Alla höftfrakturer opereras med några få undantag. Höftfraktur är den allvarligaste benskörhetsfrakturen eftersom den är förenad med ökad dödlighet. Tidigare forskning har visat att 25-30 % av patienterna aldrig kan återvända till eget boende och prognosen är särskilt dålig för patienter med nedsatt minnesfunktion eller konstaterad demenssjukdom.
Vid jämförelse med friska äldre i samma åldersgrupp är det en högre andel av höftfrakturpatienterna som är underviktiga dvs de har ett lågt body mass index (BMI). Detta kan vara ett tecken på undernäring och lågt BMI är en riskfaktor för osteoporos. Ytterligare viktnedgång månaderna efter höftfrakturen är vanlig, förlust av benvävnad och muskelmassa i samband med detta har påvisats. Muskelförlust kan vara förenat med svaghet som i sin tur kan leda till försämrad funktion och livskvalitet.

Det övergripande syftet med avhandlingen var att studera ett eventuellt samband mellan kroppsvikt och prognos efter höftfraktur hos äldre. Vi undersökte också effekterna av interventionsbehandling med läkemedel mot benskörhet och extra näringstillförsel efter höftfraktur. Dessutom studerades faktorer som hade samband med bibehållen gångförmåga och funktion hos patienter med nedsatt minnesfunktion, också det efter höftfraktur.

I studie **I** ingick 843 patienter över 65 år med höftfraktur. Alla patienter kom från eget boende, de var gångare innan frakturen och hade ingen uttalad minnespåverkan. Sambandet mellan BMI, 1-års dödlighet och förmågan att återvända till sitt hem ett år efter höftfraktur undersöktes. Resultaten visade att övervikt var positivt hos denna specifika grupp av patienter. Högt BMI var förenat med en ökad 1-årsöverlevnad och en större sannolikhet att ha återvänt till sitt hem ett år efter frakturen.

I studie **II** ingick 79 män och kvinnor med höftfraktur, som var gångare före frakturen och kom från eget boende. Patienterna delades in i tre behandlingsgrupper genom lottning. Den ena gruppen fick ett protein-och energirikt näringstillskott dagligen i 6 månader efter frakturen, som tillägg till etablerad läkemedelsbehandling mot benskörhet. Den andra gruppen fick benskörhets- behandling och den tredje gruppen utgjorde kontrollgrupp. Patienterna följdes upp under ett år och resultaten påvisade en positiv effekt på bentätheten hos den grupp av patienter som fått extra näring.

I studie **III** ingick samma patienter som i studie **II** men här utvärderades effekten av behandling med det protein-och energirika näringstillskottet på muskelmassan, handstyrkan och den hälsorelaterade livskvaliteten. Resultaten visade att den grupp som fått näringstillskott förlorade lika mycket muskelmassa som de övriga två grupperna men en antydd positiv effekt på handstyrka och hälsorelaterad livskvalitet påvisades.

I studie **IV** ingick 246 patienter med höftfraktur och nedsatt minnesfunktion eller demenssjukdom. Patienterna följdes upp efter 4 och 12 månader avseende gångförmåga och förmågan att klara dagliga basala aktiviteter som till exempel påklädning, toalettbesök och födointag. Resultaten visade att vistelse på rehabiliteringsenhet hade ett samband med bevarad gångförmåga och för förmågan att klara dagliga aktiviter för denna grupp av patienter med nedsatt minnesfunktion. Andra faktorer såsom gång -och funktionsförmåga innan skadan hade betydelse för funktionen efter ett år. Dessutom visade resultaten att patienter som skrivits ut till rehabiliteringsklinik i mindre utsträckning var rullstolsbundna.

8 ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to all of you who had any part in this work. I especially want to thank:

Margareta Hedström my main supervisor, for your constant support, guidance and for sharing your scientific and clinical knowledge with me.

Tommy Cederholm my co-supervisor, for all your valuable advice and for your excellence in science and writing.

Johan Lökk my co-supervisor, for co-authorship and encouragement

Maria Sääf co-author, for sharing your expertise in endocrinology

Amer Al-Ani co-author, for your support and guidance in the beginning of my PhD-process

Paul Ackermann, Nils Dalén, Wilhelmina Ekström, Agnes Laurin, Eva Samnegård, Anita Söderqvist for good collaboration as co-authors

Paula Kelly-Pettersson, Kristina Källbom, Åsa Norling and Bodil Samuelsson for the work with data collection

Inga Klarin my mentor and dear colleague at the Clinic of Geriatric Medicine, Karolinska University Hospital Huddinge for all your encouragement, support and wise thoughts.

All the colleagues and co-workers at the Clinic of Geriatric Medicine for your encouragement and for covering for me when I have been working with my research

My friends and closest relatives, for true love and support in different aspects of life and for being the persons you are.

Special thanks to my daughters Cecilia and Elin, for your kindness and patience. I promise to clear away books and documents from the kitchen table.

Financial support was provided by Karolinska Institutet funding (KID) and through the regional agreement on medical training and clinical research (ALF) between Stockholm County Council and Karolinska Institutet.

9 REFERENCES

1. The Swedish National Hip Fracture Registry (Rikshöft). http://www.rikshoft.se. Last modified July 2013.

2. Akesson K. Bone and joint diseases around the world. Sweden: a brief update on burden and priority. *The Journal of rheumatology. Supplement.* Aug 2003;67:38-40.

3. Nilson F, Moniruzzaman S, Gustavsson J, Andersson R. Trends in hip fracture incidence rates among the elderly in Sweden 1987-2009. *Journal of public health.* Mar 2013;35(1):125-131.

4. Jarnlo GB, Thorngren KG. Background factors to hip fractures. *Clinical orthopaedics and related research.* Feb 1993(287):41-49.

5. Bentler SE, Liu L, Obrizan M, et al. The aftermath of hip fracture: discharge placement, functional status change, and mortality. *American journal of epidemiology.* Nov 15 2009;170(10):1290-1299.

6. Magaziner J, Hawkes W, Hebel JR, et al. Recovery from hip fracture in eight areas of function. *J Gerontol A Biol Sci Med Sci.* Sep 2000;55(9):M498-507.

7. Michaelsson K, Nordstrom P, Nordstrom A, et al. Impact of hip fracture on mortality: a cohort study in hip fracture discordant identical twins. *Journal of bone and mineral research.* Feb 2014;29(2):424-431.

8. Omsland TK, Emaus N, Tell GS, et al. Mortality following the first hip fracture in Norwegian women and men (1999-2008). A NOREPOS study. *Bone.* Jun 2014;63:81-86.

9. Roche JJ, Wenn RT, Sahota O, Moran CG. Effect of comorbidities and postoperative complications on mortality after hip fracture in elderly people: prospective observational cohort study. *BMJ.* Dec 10 2005;331(7529):1374.

10. Castronuovo E, Pezzotti P, Franzo A, Di Lallo D, Guasticchi G. Early and late mortality in elderly patients after hip fracture: a cohort study using administrative health databases in the Lazio region, Italy. *BMC Geriatr.* 2011;11:37.

11. Soderqvist A, Miedel R, Ponzer S, Tidermark J. The influence of cognitive function on outcome after a hip fracture. *The Journal of bone and joint surgery. American volume.* Oct 2006;88(10):2115-2123.

12. Radinovic KS, Markovic-Denic L, Dubljanin-Raspopovic E, Marinkovic J, Jovanovic LB, Bumbasirevic V. Effect of the overlap syndrome of depressive symptoms and delirium on outcomes in elderly adults with hip fracture: a prospective cohort study. *Journal of the American Geriatrics Society.* Sep 2014;62(9):1640-1648.

13. Licata AA WS. *A DXA Primer for the Practicing Clinician: A Case-Based Manual for Understanding and Interpreting Bone Densitometry.*2014.

14. Kanis JA. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO Study Group. *Osteoporosis international.* Nov 1994;4(6):368-381.

15. Heymsfield SB. *Human Body Composition*. 2. ed. Champaign ed. Champaign, IL: Human Kinetics 2005.

16. Kanis JA, Borgstrom F, De Laet C, et al. Assessment of fracture risk. *Osteoporosis international.* Jun 2005;16(6):581-589.

17. Janssen I, Heymsfield SB, Wang ZM, Ross R. Skeletal muscle mass and distribution in 468 men and women aged 18-88 yr. *J Appl Physiol (1985).* Jul 2000;89(1):81-88.

18. Soenen S, Chapman IM. Body weight, anorexia, and undernutrition in older people. *Journal of the American Medical Directors Association.* Sep 2013;14(9):642-648.

19. World Health Organization (WHO); BMI classification. 2012; http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi.

20. Volkert D, Berner YN, Berry E, et al. ESPEN Guidelines on Enteral Nutrition: Geriatrics. *Clin Nutr.* Apr 2006;25(2):330-360.

21. Näring för god vård och omsorg. A summery in English is available. 2011; http://www.socialstyrelsen.se.

22. Lumbers M, New SA, Gibson S, Murphy MC. Nutritional status in elderly female hip fracture patients: comparison with an age-matched home living group attending day centres. *The British journal of nutrition.* Jun 2001;85(6):733-740.

23. Hung LW, Tseng WJ, Huang GS, Lin J. High short-term and long-term excess mortality in geriatric patients after hip fracture: a prospective cohort study in Taiwan. *BMC musculoskeletal disorders.* 2014;15:151.

24. Hommel A, Bjorkelund KB, Thorngren KG, Ulander K. Nutritional status among patients with hip fracture in relation to pressure ulcers. *Clin Nutr.* Oct 2007;26(5):589-596.

25. Bell JJ, Bauer JD, Capra S. The malnutrition screening tool versus objective measures to detect malnutrition in hip fracture. *Journal of human nutrition and dietetics.* Dec 2013;26(6):519-526.

26. Eneroth M, Olsson U-B, Thorngren K-G, et al. Insufficient fluid and energy intake in hospitalised patients with hip fracture. A prospective randomised study of 80 patients. *Clinical nutrition (Edinburgh, Scotland).* 2005;24(2):297-303.

27. Chevalley T, Hoffmeyer P, Bonjour JP, Rizzoli R. Early serum IGF-I response to oral protein supplements in elderly women with a recent hip fracture. *Clin Nutr.* Feb 2010;29(1):78-83.

28. Noel M, Chevenne D, Porquet D. Utility of insulin-like growth factor-I and its binding protein assays. *Current opinion in clinical nutrition and metabolic care.* Sep 2001;4(5):399-405.

29. Guerra-Menendez L, Sadaba MC, Puche JE, et al. IGF-I increases markers of osteoblastic activity and reduces bone resorption via osteoprotegerin and RANK-ligand. *Journal of translational medicine.* 2013;11:271.

30. Livingstone C. Insulin-like growth factor-I (IGF-I) and clinical nutrition. *Clinical science (London, England : 1979).* Sep 2013;125(6):265-280.

31. Yu H, Mistry J, Nicar MJ, et al. Insulin-like growth factors (IGF-I, free IGF-I and IGF-II) and insulin-like growth factor binding proteins (IGFBP-2, IGFBP-3, IGFBP-6, and ALS) in blood circulation. *Journal of clinical laboratory analysis.* 1999;13(4):166-172.

32. Lamberts SW, van den Beld AW, van der Lely AJ. The endocrinology of aging. *Science.* Oct 17 1997;278(5337):419-424.

33. Hedstrom M. Hip fracture patients, a group of frail elderly people with low bone mineral density, muscle mass and IGF-I levels. *Acta Physiologica.* 1999;167(4):347-347.

34. Naylor K, Eastell R. Bone turnover markers: use in osteoporosis. *Nat Rev Rheumatol.* 2012;8(7):379-389.

35. Vasikaran S, Cooper C, Eastell R, et al. International Osteoporosis Foundation and International Federation of Clinical Chemistry and Laboratory Medicine position on bone marker standards in osteoporosis. *Clinical chemistry and laboratory medicine.* Aug 2011;49(8):1271-1274.

36. Akesson K, Kakonen SM, Josefsson PO, Karlsson MK, Obrant KJ, Pettersson K. Fracture-induced changes in bone turnover: a potential confounder in the use of biochemical markers in osteoporosis. *J Bone Miner Metab.* 2005;23(1):30-35.

37. Ivaska KK, Gerdhem P, Akesson K, Garnero P, Obrant KJ. Effect of fracture on bone turnover markers: a longitudinal study comparing marker levels before and after injury in 113 elderly women. *Journal of bone and mineral research.* Aug 2007;22(8):1155-1164.

38. Hughes VA, Frontera WR, Roubenoff R, Evans WJ, Singh MA. Longitudinal changes in body composition in older men and women: role of body weight change and physical activity. *The American journal of clinical nutrition.* Aug 2002;76(2):473-481.

39. Fox KM, Magaziner J, Hawkes WG, et al. Loss of Bone Density and Lean Body Mass after Hip Fracture. *Osteoporosis International.* 2000;11(1):31-35.

40. Karlsson M, Nilsson JA, Sernbo I, et al. Changes of bone mineral mass and soft tissue composition after hip fracture. *Bone.* 1996;18(1):19-22.

41. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing.* Jul 2010;39(4):412-423.

42. Cederholm T, Morley JE. Sarcopenia: the new definitions. *Current opinion in clinical nutrition and metabolic care.* Sep 9 2014.

43. Landi F, Liperoti R, Russo A, et al. Sarcopenia as a risk factor for falls in elderly individuals: results from the ilSIRENTE study. *Clin Nutr.* Oct 2012;31(5):652-658.

44. Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *Journal of the American Geriatrics Society.* May 2002;50(5):889-896.

45. Tidermark J, Zethraeus N, Svensson O, Tornkvist H, Ponzer S. Femoral neck fractures in the elderly: functional outcome and quality of life according to EuroQol. *Quality of life research.* Aug 2002;11(5):473-481.

46. Laviano A, Gori C, Rianda S. Sarcopenia and nutrition. *Advances in food and nutrition research.* 2014;71:101-136.

47. Di Monaco M, Castiglioni C, Vallero F, Di Monaco R, Tappero R. Sarcopenia is more prevalent in men than in women after hip fracture: a cross-sectional study of 591 inpatients. *Archives of gerontology and geriatrics.* Sep-Oct 2012;55(2):e48-52.

48. Hida T, Ishiguro N, Shimokata H, et al. High prevalence of sarcopenia and reduced leg muscle mass in Japanese patients immediately after a hip fracture. *Geriatrics & gerontology international.* Apr 2013;13(2):413-420.

49. Lauretani F, Russo CR, Bandinelli S, et al. Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. *Journal of applied physiology.* Nov 2003;95(5):1851-1860.

50. Deutz NE, Bauer JM, Barazzoni R, et al. Protein intake and exercise for optimal muscle function with aging: Recommendations from the ESPEN Expert Group. *Clin Nutr.* Apr 24 2014.

51. Schurch MA, Rizzoli R, Slosman D, Vadas L, Vergnaud P, Bonjour JP. Protein supplements increase serum insulin-like growth factor-I levels and attenuate proximal femur bone loss in patients with recent hip fracture. A randomized, double-blind, placebo-controlled trial. *Annals of internal medicine.* May 15 1998;128(10):801-809.

52. Lawson RM, Doshi MK, Barton JR, Cobden I. The effect of unselected post-operative nutritional supplementation on nutritional status and clinical outcome of orthopaedic patients. *Clin Nutr.* Feb 2003;22(1):39-46.

53. Tkatch L, Rapin CH, Rizzoli R, et al. Benefits of oral protein supplementation in elderly patients with fracture of the proximal femur. *Journal of the American College of Nutrition.* Oct 1992;11(5):519-525.

54. Avenell A, Handoll HH. Nutritional supplementation for hip fracture aftercare in older people. *Cochrane database of systematic reviews (Online).* 2010(1):CD001880.

55. Watts NB, Bilezikian JP, Camacho PM, et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the diagnosis and treatment of postmenopausal osteoporosis. *Endocrine practice.* Nov-Dec 2010;16 Suppl 3:1-37.

56. Bischoff HA, Stahelin HB, Dick W, et al. Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* Feb 2003;18(2):343-351.

57. Zhu K, Austin N, Devine A, Bruce D, Prince RL. A randomized controlled trial of the effects of vitamin D on muscle strength and mobility in older women with vitamin D insufficiency. *Journal of the American Geriatrics Society.* Nov 2010;58(11):2063-2068.

58. Harris ST, Watts NB, Genant HK, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. *JAMA : the journal of the American Medical Association.* Oct 13 1999;282(14):1344-1352.

59. Masud T, McClung M, Geusens P. Reducing hip fracture risk with risedronate in elderly women with established osteoporosis. *Clinical interventions in aging.* 2009;4:445-449.

60. Boonen S, Orwoll ES, Wenderoth D, Stoner KJ, Eusebio R, Delmas PD. Once-weekly risedronate in men with osteoporosis: results of a 2-year, placebo-controlled, double-blind, multicenter study. *Journal of bone and mineral research.* Apr 2009;24(4):719-725.

61. Liberman UA, Weiss SR, Broll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. The Alendronate Phase III Osteoporosis Treatment Study Group. *The New England journal of medicine.* Nov 30 1995;333(22):1437-1443.

62. Black DM, Delmas PD, Eastell R, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *The New England journal of medicine.* May 3 2007;356(18):1809-1822.

63. Boonen S, Orwoll E, Magaziner J, et al. Once-yearly zoledronic acid in older men compared with women with recent hip fracture. *Journal of the American Geriatrics Society.* Nov 2011;59(11):2084-2090.

64. Chudyk AM, Jutai JW, Petrella RJ, Speechley M. Systematic review of hip fracture rehabilitation practices in the elderly. *Archives of physical medicine and rehabilitation.* Feb 2009;90(2):246-262.

65. Beaupre LA, Binder EF, Cameron ID, et al. Maximising functional recovery following hip fracture in frail seniors. *Best practice & research. Clinical rheumatology.* Dec 2013;27(6):771-788.

66. Stenvall M, Olofsson B, Nyberg L, Lundstrom M, Gustafson Y. Improved performance in activities of daily living and mobility after a multidisciplinary postoperative rehabilitation in older people with femoral neck fracture: a randomized controlled trial with 1-year follow-up. *Journal of rehabilitation medicine.* Apr 2007;39(3):232-238.

67. Seitz DP, Adunuri N, Gill SS, Rochon PA. Prevalence of dementia and cognitive impairment among older adults with hip fractures. *Journal of the American Medical Directors Association.* Oct 2011;12(8):556-564.

68. Bjorkelund KB, Hommel A, Thorngren KG, Lundberg D, Larsson S. Factors at admission associated with 4 months outcome in elderly patients with hip fracture. *AANA journal.* Feb 2009;77(1):49-58.

69. Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *Journal of the American Geriatrics Society.* Oct 1975;23(10):433-441.

70. Gruber-Baldini AL, Zimmerman S, Morrison RS, et al. Cognitive impairment in hip fracture patients: timing of detection and longitudinal follow-up. *Journal of the American Geriatrics Society.* Sep 2003;51(9):1227-1236.

71. Juliebo V, Krogseth M, Skovlund E, Engedal K, Wyller TB. Medical treatment predicts mortality after hip fracture. *J Gerontol A Biol Sci Med Sci.* Apr 2010;65(4):442-449.

72. Rolland Y, Pillard F, Lauwers-Cances V, Busquere F, Vellas B, Lafont C. Rehabilitation outcome of elderly patients with hip fracture and cognitive impairment. *Disability and rehabilitation.* Apr 8 2004;26(7):425-431.

73. Owens WD, Felts JA, Spitznagel EL, Jr. ASA physical status classifications: a study of consistency of ratings. *Anesthesiology.* Oct 1978;49(4):239-243.

74. Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW. Studies of illness in the aged. The index of ADL: A standardized measure of biological and psychosocial function. *JAMA : the journal of the American Medical Association.* Sep 21 1963;185:914-919.

75. Bang P, Eriksson U, Sara V, Wivall IL, Hall K. Comparison of acid ethanol extraction and acid gel filtration prior to IGF-I and IGF-II radioimmunoassays: improvement of determinations in acid ethanol extracts by the use of truncated IGF-I as radioligand. *Acta endocrinologica.* Jun 1991;124(6):620-629.

76. Hilding A, Hall K, Wivall-Helleryd IL, Saaf M, Melin AL, Thoren M. Serum levels of insulin-like growth factor I in 152 patients with growth hormone deficiency, aged 19-82 years, in relation to those in healthy subjects. *The Journal of clinical endocrinology and metabolism.* Jun 1999;84(6):2013-2019.

77. Unden AL, Elofsson S, Knox S, Lewitt MS, Brismar K. IGF-I in a normal population: relation to psychosocial factors. *Clinical endocrinology.* Dec 2002;57(6):793-803.

78. Bjorgul K, Novicoff WM, Saleh KJ. American Society of Anesthesiologist Physical Status score may be used as a comorbidity index in hip fracture surgery. *The Journal of arthroplasty.* Sep 2010;25(6 Suppl):134-137.

79. Donegan DJ, Gay AN, Baldwin K, Morales EE, Esterhai JL, Jr., Mehta S. Use of medical comorbidities to predict complications after hip fracture surgery in the elderly. *The Journal of bone and joint surgery. American volume.* Apr 2010;92(4):807-813.

80. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of psychiatric research.* Nov 1975;12(3):189-198.

81. Smith MJ, Breitbart WS, Platt MM. A critique of instruments and methods to detect, diagnose, and rate delirium. *Journal of pain and symptom management.* Jan 1995;10(1):35-77.

82. Dolan P. Modeling valuations for EuroQol health states. *Medical care.* Nov 1997;35(11):1095-1108.

83. Burstrom K, Johannesson M, Diderichsen F. Swedish population health-related quality of life results using the EQ-5D. *Quality of life research.* 2001;10(7):621-635.

84. Tidermark J, Bergstrom G. Responsiveness of the EuroQol (EQ-5D) and the Nottingham Health Profile (NHP) in elderly patients with femoral neck fractures. *Quality of life research.* Mar 2007;16(2):321-330.

85. Bohannon RW, Schaubert KL. Test-retest reliability of grip-strength measures obtained over a 12-week interval from community-dwelling elders. *Journal of hand therapy.* Oct-Dec 2005;18(4):426-427, quiz 428.

86. Peolsson A, Hedlund R, Oberg B. Intra- and inter-tester reliability and reference values for hand strength. *Journal of rehabilitation medicine.* Jan 2001;33(1):36-41.

87. Roberts HC, Syddall HE, Cooper C, Aihie Sayer A. Is grip strength associated with length of stay in hospitalised older patients admitted for rehabilitation? Findings from the Southampton grip strength study. *Age Ageing.* Sep 2012;41(5):641-646.

88. Lu Y, Fuerst T, Hui S, Genant HK. Standardization of bone mineral density at femoral neck, trochanter and Ward's triangle. *Osteoporosis international.* 2001;12(6):438-444.

89. The International Society for Clinical Densitometry 2012; http://www.iscd.org/resources/calculators/precision-calculator/faq/, Last modified Dec 30, 2012.

90. Schutz Y, Kyle UU, Pichard C. Fat-free mass index and fat mass index percentiles in Caucasians aged 18-98 y. *International journal of obesity and related metabolic disorders.* Jul 2002;26(7):953-960.

91. Kyle UG, Schutz Y, Dupertuis YM, Pichard C. Body composition interpretation. Contributions of the fat-free mass index and the body fat mass index. *Nutrition (Burbank, Los Angeles County, Calif.).* Jul-Aug 2003;19(7-8):597-604.

92. Baumgartner RN, Koehler KM, Gallagher D, et al. Epidemiology of sarcopenia among the elderly in New Mexico. *American journal of epidemiology.* Apr 15 1998;147(8):755-763.

93. Newman AB, Kupelian V, Visser M, et al. Sarcopenia: alternative definitions and associations with lower extremity function. *Journal of the American Geriatrics Society.* Nov 2003;51(11):1602-1609.

94. Lohman M, Tallroth K, Kettunen JA, Marttinen MT. Reproducibility of dual-energy x-ray absorptiometry total and regional body composition measurements using different scanning positions and definitions of regions. *Metabolism: clinical and experimental.* Nov 2009;58(11):1663-1668.

95. Andridge RR, Little RJ. A Review of Hot Deck Imputation for Survey Non-response. *International statistical review.* Apr 2010;78(1):40-64.

96. Declaration of Helsinki. 2014; http://www.wma.net/en/30publications/10policies/b3/.

97. Flodin L, Svensson S, Cederholm T. Body mass index as a predictor of 1 year mortality in geriatric patients. *Clin Nutr.* Apr 2000;19(2):121-125.

98. Weiss A, Beloosesky Y, Boaz M, Yalov A, Kornowski R, Grossman E. Body mass index is inversely related to mortality in elderly subjects. *Journal of general internal medicine.* Jan 2008;23(1):19-24.

99. Dahl AK, Fauth EB, Ernsth-Bravell M, Hassing LB, Ram N, Gerstof D. Body mass index, change in body mass index, and survival in old and very old persons. *Journal of the American Geriatrics Society.* Apr 2013;61(4):512-518.

100. Meyer HE, Tverdal A, Falch JA. Body height, body mass index, and fatal hip fractures: 16 years' follow-up of 674,000 Norwegian women and men. *Epidemiology.* May 1995;6(3):299-305.

101. Prieto-Alhambra D, Premaor MO, Aviles FF, et al. Relationship between mortality and BMI after fracture: a population-based study of men and women aged >/=40 years. *Journal of bone and mineral research.* Aug 2014;29(8):1737-1744.

102. Thourani VH, Keeling WB, Kilgo PD, et al. The impact of body mass index on morbidity and short- and long-term mortality in cardiac valvular surgery. *The Journal of thoracic and cardiovascular surgery.* Nov 2011;142(5):1052-1061.

103. Singh JA, Sperling JW, Cofield RH. Ninety day mortality and its predictors after primary shoulder arthroplasty: an analysis of 4,019 patients from 1976-2008. *BMC musculoskeletal disorders.* 2011;12:231.

104. Garcia-Ptacek S, Kareholt I, Farahmand B, Cuadrado ML, Religa D, Eriksdotter M. Body-mass index and mortality in incident dementia: a cohort study on 11,398 patients from SveDem, the Swedish Dementia Registry. *Journal of the American Medical Directors Association.* Jun 2014;15(6):447 e441-447.

105. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. *JAMA : the journal of the American Medical Association.* Jan 2 2013;309(1):71-82.

106. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW, Jr. Body-mass index and mortality in a prospective cohort of U.S. adults. *The New England journal of medicine.* Oct 7 1999;341(15):1097-1105.

107. Must A, Spadano J, Coakley EH, Field AE, Colditz G, Dietz WH. The disease burden associated with overweight and obesity. *JAMA : the journal of the American Medical Association.* Oct 27 1999;282(16):1523-1529.

108. Standl E, Erbach M, Schnell O. Defending the con side: obesity paradox does not exist. *Diabetes care.* Aug 2013;36 Suppl 2:S282-286.

109. Oreopoulos A, Kalantar-Zadeh K, Sharma AM, Fonarow GC. The obesity paradox in the elderly: potential mechanisms and clinical implications. *Clinics in geriatric medicine.* Nov 2009;25(4):643-659, viii.

110. Hebuterne X, Bermon S, Schneider SM. Ageing and muscle: the effects of malnutrition, re-nutrition, and physical exercise. *Current opinion in clinical nutrition and metabolic care.* Jul 2001;4(4):295-300.

111. Ljungqvist O, Soop M, Hedstrom M. Why metabolism matters in elective orthopedic surgery: a review. *Acta orthopaedica.* Oct 2007;78(5):610-615.

112. Bachrach-Lindstrom MA, Ek AC, Unosson M. Nutritional state and functional capacity among elderly Swedish people with acute hip fracture. *Scandinavian journal of caring sciences.* 2000;14(4):268-274.

113. Ponzer S, Tidermark J, Brismar K, Soderqvist A, Cederholm T. Nutritional status, insulin-like growth factor-1 and quality of life in elderly women with hip fractures. *Clin Nutr.* Aug 1999;18(4):241-246.

114. Batsis JA, Huddleston JM, Melton LJt, et al. Body mass index and risk of adverse cardiac events in elderly patients with hip fracture: a population-based study. *Journal of the American Geriatrics Society.* Mar 2009;57(3):419-426.

115. Haleem S, Lutchman L, Mayahi R, Grice JE, Parker MJ. Mortality following hip fracture: trends and geographical variations over the last 40 years. *Injury.* Oct 2008;39(10):1157-1163.

116. Hommel A, Ulander K, Bjorkelund KB, Norrman PO, Wingstrand H, Thorngren KG. Influence of optimised treatment of people with hip fracture on time to operation, length of hospital stay, reoperations and mortality within 1 year. *Injury.* Oct 2008;39(10):1164-1174.

117. Tarazona-Santabalbina FJ, Belenguer-Varea A, Rovira Daudi E, et al. Severity of cognitive impairment as a prognostic factor for mortality and functional recovery of geriatric patients with hip fracture. *Geriatrics & gerontology international.* Aug 27 2014.

118. Neuman MD, Silber JH, Magaziner JS, Passarella MA, Mehta S, Werner RM. Survival and functional outcomes after hip fracture among nursing home residents. *JAMA internal medicine.* Aug 2014;174(8):1273-1280.

119. Aharonoff GB, Barsky A, Hiebert R, Zuckerman JD, Koval KJ. Predictors of discharge to a skilled nursing facility following hip fracture surgery in New York State. *Gerontology.* Sep-Oct 2004;50(5):298-302.

120. Reider L, Hawkes W, Hebel JR, et al. The association between body mass index, weight loss and physical function in the year following a hip fracture. *J Nutr Health Aging.* Jan 2013;17(1):91-95.

121. Stuck AE, Walthert JM, Nikolaus T, Bula CJ, Hohmann C, Beck JC. Risk factors for functional status decline in community-living elderly people: a systematic literature review. *Social science & medicine (1982).* Feb 1999;48(4):445-469.

122. Volpato S, Onder G, Cavalieri M, et al. Characteristics of nondisabled older patients developing new disability associated with medical illnesses and hospitalization. *Journal of general internal medicine.* May 2007;22(5):668-674.

123. Hedstrom M, Saaf M, Dalen N. Low IGF-I levels in hip fracture patients. A comparison of 20 coxarthrotic and 23 hip fracture patients. *Acta orthopaedica Scandinavica.* Apr 1999;70(2):145-148.

124. Miller MD, Crotty M, Whitehead C, Bannerman E, Daniels LA. Nutritional supplementation and resistance training in nutritionally at risk older adults following lower limb fracture: a randomized controlled trial. *Clin Rehabil.* Apr 2006;20(4):311-323.

125. Lee CG, Boyko EJ, Nielson CM, et al. Mortality risk in older men associated with changes in weight, lean mass, and fat mass. *Journal of the American Geriatrics Society.* Feb 2011;59(2):233-240.

126. Berger C, Langsetmo L, Joseph L, et al. Association between change in BMD and fragility fracture in women and men. *Journal of bone and mineral research.* Feb 2009;24(2):361-370.

127. Hannan MT, Tucker KL, Dawson-Hughes B, Cupples LA, Felson DT, Kiel DP. Effect of dietary protein on bone loss in elderly men and women: the Framingham Osteoporosis Study. *Journal of bone and mineral research.* Dec 2000;15(12):2504-2512.

128. Meng X, Zhu K, Devine A, Kerr DA, Binns CW, Prince RL. A 5-year cohort study of the effects of high protein intake on lean mass and BMC in elderly postmenopausal women. *Journal of bone and mineral research.* Nov 2009;24(11):1827-1834.

129. Arnett T. Regulation of bone cell function by acid-base balance. *The Proceedings of the Nutrition Society.* May 2003;62(2):511-520.

130. Hunt JR, Johnson LK, Fariba Roughead ZK. Dietary protein and calcium interact to influence calcium retention: a controlled feeding study. *The American journal of clinical nutrition.* May 2009;89(5):1357-1365.

131. Hampson G, Martin FC, Moffat K, et al. Effects of dietary improvement on bone metabolism in elderly underweight women with osteoporosis: a randomised controlled trial. *Osteoporosis international.* Sep 2003;14(9):750-756.

132. Osaki M, Tatsuki K, Hashikawa T, et al. Beneficial effect of risedronate for preventing recurrent hip fracture in the elderly Japanese women. *Osteoporosis international.* Feb 2012;23(2):695-703.

133. Eriksen EF, Lyles KW, Colon-Emeric CS, et al. Antifracture efficacy and reduction of mortality in relation to timing of the first dose of zoledronic acid after hip fracture. *Journal of bone and mineral research.* Jul 2009;24(7):1308-1313.

134. Burden AM, Paterson JM, Solomon DH, Mamdani M, Juurlink DN, Cadarette SM. Bisphosphonate prescribing, persistence and cumulative exposure in Ontario, Canada. *Osteoporosis international.* Mar 2012;23(3):1075-1082.

135. Cotte FE, Fardellone P, Mercier F, Gaudin AF, Roux C. Adherence to monthly and weekly oral bisphosphonates in women with osteoporosis. *Osteoporosis international.* Jan 2010;21(1):145-155.

136. Tengstrand B, Cederholm T, Söderqvist A, et al. Effects of protein-rich supplementation and nandrolone on bone tissue after a hip fracture. *Clinical Nutrition.* 2007;26(4):460-465.

137. DeLappe E, McGreevy C, ni Chadhain N, Grimes H, O'Brien T, Mulkerrin E. Vitamin D insufficiency in older female community-dwelling acute hospital admissions and the response to supplementation. *Eur J Clin Nutr.* Aug 2006;60(8):1009-1015.

138. Verreijen AM, Verlaan S, Engberink MF, Swinkels S, de Vogel-van den Bosch J, Weijs PJ. A high whey protein-, leucine-, and vitamin D-enriched supplement preserves muscle mass during intentional weight loss in obese older adults: a double-blind randomized controlled trial. *The American journal of clinical nutrition.* Feb 2015;101(2):279-286.

139. Muir SW, Montero-Odasso M. Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis. *Journal of the American Geriatrics Society.* Dec 2011;59(12):2291-2300.

140. Knutsen KV, Madar AA, Lagerlov P, et al. Does vitamin D improve muscle strength in adults? A randomized, double-blind, placebo-controlled trial among ethnic minorities in Norway. *The Journal of clinical endocrinology and metabolism.* Jan 2014;99(1):194-202.

141. Diekmann R, Winning K, Bauer JM, et al. Vitamin D status and physical function in nursing home residents: a 1-year observational study. *Zeitschrift fur Gerontologie und Geriatrie.* Jul 2013;46(5):403-409.

142. Tidermark J, Ponzer S, Carlsson P, et al. Effects of protein-rich supplementation and nandrolone in lean elderly women with femoral neck fractures. *Clin Nutr.* Aug 2004;23(4):587-596.

143. Patterson BM, Cornell CN, Carbone B, Levine B, Chapman D. Protein depletion and metabolic stress in elderly patients who have a fracture of the hip. *The Journal of bone and joint surgery. American volume.* Feb 1992;74(2):251-260.

144. Drevet S, Bioteau C, Maziere S, et al. Prevalence of protein-energy malnutrition in hospital patients over 75 years of age admitted for hip fracture. *Orthopaedics & traumatology, surgery & research : OTSR.* Oct 2014;100(6):669-674.

145. Bell J, Bauer J, Capra S, Pulle CR. Barriers to nutritional intake in patients with acute hip fracture: time to treat malnutrition as a disease and food as a medicine? *Canadian journal of physiology and pharmacology.* Jun 2013;91(6):489-495.

146. Kim HK, Suzuki T, Saito K, et al. Effects of exercise and amino acid supplementation on body composition and physical function in community-dwelling elderly Japanese sarcopenic women: a randomized controlled trial. *Journal of the American Geriatrics Society.* Jan 2012;60(1):16-23.

147. Stout JR, Smith-Ryan AE, Fukuda DH, et al. Effect of calcium beta-hydroxy-beta-methylbutyrate (CaHMB) with and without resistance training in men and women 65+yrs: a randomized, double-blind pilot trial. *Experimental gerontology.* Nov 2013;48(11):1303-1310.

148. Aronsson A, Al-Ani NA, Brismar K, Hedstrom M. A carbohydrate-rich drink shortly before surgery affected IGF-I bioavailability after a total hip replacement. A double-blind placebo controlled study on 29 patients. *Aging clinical and experimental research.* Apr 2009;21(2):97-101.

149. Tieland M, Dirks ML, van der Zwaluw N, et al. Protein supplementation increases muscle mass gain during prolonged resistance-type exercise training in frail elderly people: a randomized, double-blind, placebo-controlled trial. *Journal of the American Medical Directors Association.* Oct 2012;13(8):713-719.

150. Cederholm TE, Hellstrom KH. Reversibility of protein-energy malnutrition in a group of chronically-ill elderly outpatients. *Clin Nutr.* Apr 1995;14(2):81-87.

151. Price R, Daly F, Pennington CR, McMurdo ME. Nutritional supplementation of very old people at hospital discharge increases muscle strength: a randomised controlled trial. *Gerontology.* May-Jun 2005;51(3):179-185.

152. Goodpaster BH, Park SW, Harris TB, et al. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. *J Gerontol A Biol Sci Med Sci.* Oct 2006;61(10):1059-1064.

153. Tieland M, van de Rest O, Dirks ML, et al. Protein supplementation improves physical performance in frail elderly people: a randomized, double-blind, placebo-controlled trial. *Journal of the American Medical Directors Association.* Oct 2012;13(8):720-726.

154. Di Monaco M, Castiglioni C, De Toma E, et al. Handgrip strength but not appendicular lean mass is an independent predictor of functional outcome in hip-fracture women: a short-term prospective study. *Archives of physical medicine and rehabilitation.* Sep 2014;95(9):1719-1724.

155. Savino E, Martini E, Lauretani F, et al. Handgrip strength predicts persistent walking recovery after hip fracture surgery. *The American journal of medicine.* Dec 2013;126(12):1068-1075 e1061.

156. Di Monaco M, Castiglioni C, De Toma E, Gardin L, Giordano S, Tappero R. Handgrip Strength is an Independent Predictor of Functional Outcome in Hip-Fracture Women: A Prospective Study With 6-Month Follow-Up. *Medicine.* Feb 2015;94(6):e542.

157. Ekstrom W, Miedel R, Ponzer S, Hedstrom M, Samnegard E, Tidermark J. Quality of life after a stable trochanteric fracture--a prospective cohort study on 148 patients. *Journal of orthopaedic trauma.* Jan 2009;23(1):39-44.

158. Bruce D, Laurance I, McGuiness M, Ridley M, Goldswain P. Nutritional supplements after hip fracture: poor compliance limits effectiveness. *Clin Nutr.* Oct 2003;22(5):497-500.

159. Miller MD, Daniels LA, Bannerman E, Crotty M. Adherence to nutrition supplements among patients with a fall-related lower limb fracture. *Nutrition in clinical practice.* Oct 2005;20(5):569-578.

160. Beloosesky Y, Grinblat J, Epelboym B, Weiss A, Grosman B, Hendel D. Functional gain of hip fracture patients in different cognitive and functional groups. *Clin Rehabil.* May 2002;16(3):321-328.

161. Hershkovitz A, Kalandariov Z, Hermush V, Weiss R, Brill S. Factors affecting short-term rehabilitation outcomes of disabled elderly patients with proximal hip fracture. *Archives of physical medicine and rehabilitation.* Jul 2007;88(7):916-921.

162. Zuckerman JD, Sakales SR, Fabian DR, Frankel VH. Hip fractures in geriatric patients. Results of an interdisciplinary hospital care program. *Clinical orthopaedics and related research.* Jan 1992(274):213-225.

163. Stenvall M, Olofsson B, Lundstrom M, et al. A multidisciplinary, multifactorial intervention program reduces postoperative falls and injuries after femoral neck fracture. *Osteoporosis international.* Feb 2007;18(2):167-175.

164. McGilton KS, Mahomed N, Davis AM, Flannery J, Calabrese S. Outcomes for older adults in an inpatient rehabilitation facility following hip fracture (HF) surgery. *Archives of gerontology and geriatrics.* Jul-Aug 2009;49(1):e23-31.

165. Huusko TM, Karppi P, Avikainen V, Kautiainen H, Sulkava R. Randomised, clinically controlled trial of intensive geriatric rehabilitation in patients with hip fracture: subgroup analysis of patients with dementia. *BMJ (Clinical research ed.).* Nov 4 2000;321(7269):1107-1111.

166. Stenvall M, Berggren M, Lundstrom M, Gustafson Y, Olofsson B. A multidisciplinary intervention program improved the outcome after hip fracture for people with dementia--subgroup analyses of a randomized controlled trial. *Archives of gerontology and geriatrics.* May-Jun 2012;54(3):e284-289.

167. Lenze EJ, Munin MC, Dew MA, et al. Adverse effects of depression and cognitive impairment on rehabilitation participation and recovery from hip fracture. *International journal of geriatric psychiatry.* May 2004;19(5):472-478.

168. Feng L, Scherer SC, Tan BY, Chan G, Fong NP, Ng TP. Comorbid cognitive impairment and depression is a significant predictor of poor outcomes in hip fracture rehabilitation. *International psychogeriatrics / IPA.* Mar 2010;22(2):246-253.

169. Seitz DP, Gill SS, Gruneir A, et al. Effects of dementia on postoperative outcomes of older adults with hip fractures: a population-based study. *Journal of the American Medical Directors Association.* May 2014;15(5):334-341.

170. Munin MC, Begley A, Skidmore ER, Lenze EJ. Influence of rehabilitation site on hip fracture recovery in community-dwelling subjects at 6-month follow-up. *Archives of physical medicine and rehabilitation.* Jul 2006;87(7):1004-1006.

171. Beaupre LA, Cinats JG, Jones CA, et al. Does functional recovery in elderly hip fracture patients differ between patients admitted from long-term care and the community? *J Gerontol A Biol Sci Med Sci.* Oct 2007;62(10):1127-1133.

172. Crotty M, Miller M, Whitehead C, Krishnan J, Hearn T. Hip fracture treatments--what happens to patients from residential care? *Journal of quality in clinical practice.* Dec 2000;20(4):167-170.

173. Clarke A, Rosen R. Length of stay. How short should hospital care be? *European journal of public health.* Jun 2001;11(2):166-170.

174. Munin MC, Seligman K, Dew MA, et al. Effect of rehabilitation site on functional recovery after hip fracture. *Archives of physical medicine and rehabilitation.* Mar 2005;86(3):367-372.

175. Blomfeldt R, Tornkvist H, Ponzer S, Soderqvist A, Tidermark J. Internal fixation versus hemiarthroplasty for displaced fractures of the femoral neck in elderly patients with severe cognitive impairment. *The Journal of bone and joint surgery. British volume.* Apr 2005;87(4):523-529.

176. Morghen S, Gentile S, Ricci E, Guerini F, Bellelli G, Trabucchi M. Rehabilitation of older adults with hip fracture: cognitive function and walking abilities. *Journal of the American Geriatrics Society.* Aug 2011;59(8):1497-1502.

177. Dubljanin-Raspopovic E, Markovic-Denic L, Matanovic D, Grajic M, Krstic N, Bumbasirevic M. Is pre-fracture functional status better than cognitive level in predicting short-term outcome of elderly hip fracture patients? *Archives of medical science : AMS.* Feb 29 2012;8(1):115-122.

178. Magaziner J, Simonsick EM, Kashner TM, Hebel JR. Patient-proxy response comparability on measures of patient health and functional status. *Journal of clinical epidemiology.* 1988;41(11):1065-1074.

179. Blomqvist K, Hallberg IR. Pain in older adults living in sheltered accommodation--agreement between assessments by older adults and staff. *Journal of clinical nursing.* Mar 1999;8(2):159-169.

180. Soderqvist A, Ekstrom W, Ponzer S, et al. Prediction of mortality in elderly patients with hip fractures: a two-year prospective study of 1,944 patients. *Gerontology.* 2009;55(5):496-504.