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# QUALITY OF LIFE AND FEMORAL NECK FRACTURES

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To my family

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## ABSTRACT

The worldwide increase in hip fractures is a major challenge to the health care system and society. The proper treatment of femoral neck fractures in the elderly is still controversial, and even more so from an international perspective. Optimising the treatment for improved outcomes and a reduced need for secondary surgery is mandatory for humanitarian and economical reasons. The importance of incorporating the patient's perspective of the outcome in clinical trials has been acknowledged and there are now numerous instruments for assessing the quality of life. We evaluated two quality of life instruments, the EQ-5D and the SF-36, in patients with femoral neck fractures and also measured the quality of life two years after different interventions.

The EQ-5D was validated in two prospective studies and it appeared to be an appropriate quality of life instrument in elderly patients with femoral neck fractures. There was a good correlation between the quality of life (EQ-5D<sub>index</sub> scores) and other outcome measures such as pain, mobility and independence in activities of daily living (ADL). The results also showed high responsiveness, i.e., ability to capture clinically important changes, for both the EQ-5D and the SF-36. The questionnaire response rate for both instruments was high.

The rated prefracture EQ-5D<sub>index</sub> scores showed good correspondence with the scores of an age-matched Swedish reference population. The quality of life in patients with femoral neck fractures treated with internal fixation (IF) decreased, particularly in patients with fracture healing complications. The fracture healing complications rate at two years in patients with displaced femoral neck fractures treated with IF was 36% compared with 7% in patients with undisplaced fractures. The quality of life of patients with uneventfully healed fractures at two year was lower in patients with primary displaced fractures than in patients with primary undisplaced fractures.

In a prospective randomised trial, patients with displaced femoral neck fractures were randomised to IF or total hip replacement (THR). IF resulted in more complications than THR, 36% versus 4%, and necessitated more reoperations, 42% versus 4%. Hip function and quality of life (EQ-5D) were generally better in the THR group. In summary, THR yielded a better outcome than IF for an elderly, relatively healthy, lucid patient with a displaced femoral neck fracture.

In a study of elderly women with femoral neck fractures, nearly half of the patients displayed signs of protein-energy malnutrition. Underweight was associated with muscle fatigue, cognitive dysfunction and a low quality of life (Nottingham Health Profile).

In a prospective randomised trial, protein-rich liquid supplementation in combination with an anabolic steroid given for 6 months to lean elderly women after a femoral neck fracture was shown to positively affect lean body mass, ADL and quality of life (EQ-5D). Fracture healing complications had a negative impact on body weight, lean body mass and quality of life.

**Key words:** Femoral neck fractures; Aged; Quality of life; Treatment outcome; Fracture fixation, internal; Arthroplasty, replacement, hip; Nutritional disorder; Anabolic steroids.

## LIST OF PAPERS

This thesis is based on the following papers, which are referred to in the text by their Roman numerals (*Studies I-VI*).

- I **Femoral Neck Fractures in the Elderly: Functional Outcome and Quality of Life According to EuroQol.**  
Tidermark J, Zethraeus N, Svensson O, Törnkvist H, Ponzer S.  
Quality of Life Research 2002; 11: 473 – 481.
- II **Quality of Life Related to Fracture Displacement among Elderly Patients with Femoral Neck Fractures Treated with Internal Fixation.**  
Tidermark J, Zethraeus N, Svensson O, Törnkvist H, Ponzer S.  
Journal of Orthopaedic Trauma 2002; 16 (1): 34 - 38.
- III **Responsiveness of the EuroQol (EQ 5-D) and the SF-36 in Elderly Patients with Displaced Femoral Neck Fractures.**  
Tidermark J, Bergström G, Svensson O, Törnkvist H, Ponzer S.  
Quality of Life Research, in press.
- IV **Internal Fixation versus Total Hip Arthroplasty for Displaced Femoral Neck Fractures – a Randomised Controlled Trial.**  
Tidermark J, Ponzer S, Svensson O, Söderqvist A, Törnkvist H.  
Journal of Bone & Joint Surgery (Br), accepted.
- V **Nutritional Status, Insulinlike Growth Factor-1 and Quality of Life in Elderly Women with Hip Fractures.**  
Ponzer S , Tidermark J, Brismar K, Söderqvist A, Cederholm T.  
Clinical Nutrition 1999; vol 18;4: 241-246.
- VI **Effects of Protein-rich Supplementation and Nandrolone in Lean Elderly Women with Femoral Neck Fractures.**  
Tidermark J, Ponzer S, Carlsson P, Söderqvist A, Brismar K, Tengstrand B, Cederholm T.  
Clinical Nutrition, submitted.

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## LIST OF ABBREVIATIONS

AMC	Arm muscle circumference
BW	Body weight
EC	External criterion
EQ-5D	The 5-dimensional scale of the EuroQol
EQ-5D <sub>index</sub> score	The quality of life score generated from the EQ-5D
HGS	Hand grip strength
HRQoL	Health-related quality of life
IF	Internal fixation
IGF-1	Insulin-like growth factor 1
IGFBP-1	IGF binding protein 1
LBM	Lean body mass
NHP	Nottingham Health Profile
PEM	Protein-energy malnutrition
RCT	Randomised controlled trial
SF-36	Short Form 36
SPMSQ	Short Portable Mental Status Questionnaire
THR	Total hip replacement
TSF	Triceps skinfold thickness
95%CI	95% Confidence interval

## INTRODUCTION

The incidence of hip fractures is increasing and the annual number worldwide is estimated to rise from 1.7 million in 1990 to 6.3 million by the year 2050 (1). This will be a major challenge to the health care system and society. Most hip fractures are related to osteoporosis (2). The cumulated risk for hip fracture is 20% for an 80-year-old woman and almost 50% for a 90-year-old woman (3). Displaced femoral neck fractures (Garden III and IV) (4) differ from undisplaced fractures (Garden I and II) and from the other main group of hip fractures, the trochanteric fractures, with regard to the high incidence of fracture healing complications. The proper surgical treatment of displaced femoral neck fractures in the elderly is still controversial in Sweden, and even more so from an international perspective. Optimising the treatment for improved outcome and a reduced need for secondary surgery is therefore mandatory.

In many studies on hip fractures, the outcome of treatment has been defined in terms of complications or specific hip scores (5-17). Quality of life as an outcome measure is rarely used. Quality of life assessment may, however, add a further dimension to conventional outcome measures, i.e. it may display the impact of the injury on other areas of life from the patient's perspective. In addition, some of the instruments, e.g. the EuroQol (EQ-5D) (18), are preference-based and generate an overall score from which it is possible to construct quality-adjusted-life years (QALYs), a measure frequently used in health economic cost-effectiveness analyses (19).

Fracture healing complications and reoperations after internal fixation (IF) of displaced femoral neck fractures are common (5-8, 10-17, 20) in spite of an improved surgical technique. Yet, IF is still recommended as primary treatment in Sweden (21). The rationale of this concept is to salvage the hip of patients in whom the fracture heals and perform secondary arthroplasties in those patients sustaining a fracture healing complication, thereby, it is thought, avoiding unnecessary surgery. Primary arthroplasties (hemi, i.e., when only the femoral component is replaced, or total, i.e., when the acetabulum also is replaced) have been more prevalent in the UK, on the European continent and in North America, no doubt partly because of economic incentives. Total hip replacement (THR) is well documented in osteoarthritis and rheumatoid arthritis and has also been used as a primary procedure in displaced femoral neck fractures (16, 20, 22-25). The major drawback after hip fracture has been the high dislocation rates (16, 20, 22, 24, 25). There are a few randomised controlled trials (RCT) (16, 17, 22, 23, 25) comparing IF and THR and none of them evaluate the quality of life. Obtaining reliable data is crucial for establishing evidence-based treatment algorithms for this vast group of patients and a new Cochrane review based on randomised trials is currently being performed (26).

Protein-energy malnutrition (PEM) is found in 30-50% of hip fracture patients (27). The combination of PEM-related factors such as muscle atrophy, lack of subcutaneous fat, and osteoporosis makes the elderly more prone to falls (28), the cushioning capacity of the subcutaneous tissue diminishes (29) and the osteoporotic skeleton fractures more easily. Poor nutritional status complicates rehabilitation after a fracture (27, 30) and postoperative rehabilitation is facilitated by actively improving nutritional intake (30, 31).

## QUALITY OF LIFE

“Quality of life is defined as an individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standard and concerns. It is a broad ranging concept affected in a complex way by the person’s physical health, psychological state, level of independence, social relationships, and their relationship to salient features of their environment.” (WHO-QOL group, 1993). This definition of quality of life emphasises the multifaceted domains of physical, psychological and social functioning. The definition of health also clearly states that health is more than just absence of disease or disability but also includes dimensions of physical health, psychological well-being and life satisfaction. Health-related quality of life compared to quality of life focuses more on the impact of a perceived health state, as a result of an injury or illness, on the ability to live a fulfilling life. The terms are often used interchangeably and, for the sake of simplicity, we hereafter will use the term quality of life.

There is a growing opinion that measures of quality of life should be used to evaluate health-care interventions (32). It is argued that what really matters is how the patient feels, rather than how doctors think they ought to feel on the basis of clinical measurements. The quality of life assessment can, then, serve as a complement to conventional outcome measures in orthopaedic surgery, such as fracture-healing complications, re-operations and mortality, and also as a complement to disease-specific outcome instruments, e.g. scores evaluating hip function.

The quality of life measures can be divided into four main categories.

1. *Dimension or domain-specific measures* that focus on particular aspects of health.
2. *Disease or population-specific measures* that focus on a particular health problem.
3. *Generic measures* that can be used across different patient populations and usually several domains, e.g. the SF-36 (33, 34) and the Nottingham Health Profile (NHP) (35).
4. *Utility measures*, which have been developed for economic evaluations, incorporate a preference for health states and produce a single index, e.g. the EuroQol (EQ-5D) (18) that can also be used to construct quality-adjusted-life years (QALYs).

The instruments used in this study cover several dimensions that partly overlap and display different aspects of the quality of life (Table 1).

**Table 1.** Dimensions of quality of life in instruments (18, 33 - 35).

<b>EQ-5D</b>	<b>SF-36</b>	<b>NHP</b>
Mobility	Physical functioning	Lack of energy
Self-care	Role limitations due to physical function	Pain
Usual activities	Bodily pain	Emotional reaction
Pain/discomfort	General health	Sleep disturbance
Anxiety/depression	Vitality	Social isolation
	Social Functioning	Physical mobility
	Role limitations due to emotional problems	
	Mental health	

## Quality of life in patients with femoral neck fractures

There are only a few studies evaluating the quality of life after a femoral neck fracture on a longer time scale. Borgquist *et al.* (36) assessed the quality of life (Nottingham Health Profile, NHP Part 1) in 61 patients with femoral neck fractures and 39 with trochanteric fractures at 6 and 12 months and compared the quality of life scores with the functional status (ADL and walking ability) at 4 months. They found that patients with poor function at 4 months after the fracture had scores indicating a lower quality of life.

Coast *et al.* (37) and Van Balen *et al.* (38) reported an improvement in the quality of life (EQ-5D and NHP) of hip fracture patients from after the fracture to the 3-4 month follow-up.

Randell *et al.* (39) examined the change in the quality of life (SF-36) in 32 hip fracture patients (type of fracture not stated). At 3 months there was a significant reduction in quality of life in the domains Physical Functioning, Vitality and Social Functioning compared to before the fracture (based on recall).

Nilsson *et al.* (40) investigated the quality of life (NHP parts I and II) more than five years after surgery in a retrospective study on two matched groups of 28 patients with femoral neck fractures treated with internal fixation or secondary total hip replacement after failed primary internal fixation. Patients with healed fractures had fewer problems with sleep, housework and hobbies, and thus functioned better than patients who had required a secondary total hip replacement. However, the retrospective designs do not allow any far-reaching conclusions.

## SURGICAL INTERVENTION

### Results after internal fixation (IF)

Fracture healing complications after femoral neck fracture in elderly patients treated with IF are common. The complications are usually divided into non-union (including early redisplacement or progressive displacement) and avascular necrosis (AVN). However, the follow-up period has to be at least two years to reveal all healing complications.

The number of secondary arthroplasties after failed internal fixation is not acceptable as a single outcome measure since the indications for an arthroplasty are nearly always relative and must be balanced against surgical risks. This decision differs between surgeons and due to local therapeutic traditions and resources. There is also a substantial risk that some of the patients with confirmed healing complications would not be reoperated on during study periods due to health care waiting-times. Additionally, some patients, especially patients with AVN, will later develop indications for hip replacement due to progressive hip disability.

Undisplaced fractures have a lower complication rate than displaced fractures in prospective studies with a two-year follow-up, ranging from 0% to 24 %, median 12% (Table 2).

In displaced fractures, the complication rate in prospective studies with a two-year follow-up ranges from 12% to 68%, median 42% (Table 3).

**Table 2.** Fracture healing complications\* and mortality\*\* in undisplaced femoral neck fractures treated with IF. Only prospective studies with at least a two-year follow-up.

First author	Year	Age***	n	Non-union (%)	AVN (%)	Mortality (%)
Strömqvist	1984	78 (52-95)	152	0	19	38
Strömqvist	1987	78 (19-98)	300	3	2	28
Elmerson	1988	79 (18-98)	223	9	7	33
Rehnberg	1989	82 (SD 8)	44	0	0	22
Holmberg	1990	79	220	9	15	28
Sernbo	1990	77 (SD 11)	410	15	6	30
Wihlborg	1990	77 (46-100)	200	7	11	25
Strömqvist	1992	78 (18-100)	626	4	3	31
Elmerson	1995	77 (50-99)	222	11	13	28
Lindequist	1995	78	72	0	0	23
<b>Median</b>		<b>78</b>	<b>221</b>	<b>5.5</b>	<b>6.5</b>	<b>28</b>

\* Percentage of healing complications in patients still alive at the two-year follow-up.

\*\* Mortality at two-years, if stated.

\*\*\* Mean and range or SD if stated in article.

**Table 3.** Fracture healing complications\* and mortality\*\* in displaced femoral neck fractures treated with IF. Only prospective studies with at least a two-year follow-up.

First author	Year	Age***	n	Non-union (%)	AVN (%)	Mortality (%)
Strömqvist	1984	78 (52-95)	152	33	19	38
Madsen	1987	75 (25-92)	104	27	8	
Strömqvist	1987	78 (19-98)	300	26	9	28
Elmerson	1988	79 (18-98)	223	46	10	33
Rehnberg	1989	82 (SD 8)	44	0	12	22
Holmberg	1990	79	220	32	13	28
Sernbo	1990	77 (SD 11)	410	49	19	30
Wihlborg	1990	77 (46-100)	200	27	11	25
Strömqvist	1992	78 (18-100)	626	30	11	31
Elmerson	1995	77 (50-99)	222	42	20	28
Lindequist	1995	78	72	36	13	23
Johansson	2000****	84 (75-96)	50	36	12	33
Rogmark	2002****	82 (SD 6)	217	28	12	21
<b>Median</b>		<b>78</b>	<b>217</b>	<b>30</b>	<b>12</b>	<b>28</b>

\* Percentage of healing complications in patients still alive at two years.

\*\* Mortality at two-years, if stated.

\*\*\* Mean and range or SD if stated in article.

\*\*\*\* Complication rate among two-year survivors not stated, figures represent detected complications in all patients available.

These data are in harmony with a well-performed meta-analysis (20) of 106 published reports on more than 6000 patients. The complication rate after displaced femoral neck fractures was 49%; early redisplacement and non-union, 33%, and AVN, 16%, and the reoperation rate was 35%. The choice of implant was analysed in a meta-analysis of 25 randomised trials in nearly 5000 patients (41). Screws appeared to be superior to pins, but it was not possible to determine the type or numbers of screws. The use of a side-plate appeared to be unnecessary.

In summary, most larger studies on displaced femoral neck fractures with a two-year follow-up report fracture-healing complications in the range of 35-50%. And although the criteria for fracture healing complications may vary somewhat, the natural history is worse than generally perceived.

### Results after total hip replacement (THR)

The main complication after a THR for a femoral neck fracture is dislocation. Deep infections are rare in studies using modern surgical routines and antibiotic prophylactics (16, 17, 22-25). There is a cumulative risk of revision due to aseptic loosening, but this risk seems to be minor from a ten-year perspective. Ninety-eight percent of Swedish hip fracture patients having undergone a THR were not revised after 11 years (42). The expected mean survival of a 70-year-old Swedish woman is 16 years and of a male 13 years (43). This is confirmed by Ravikumar *et al.* (25) who found a 13-year revision rate of 7 % after THR mainly due to recurrent dislocations and partly due to deep infections, but with no case of aseptic loosening.

Table 4 shows the number of hip complications (dislocation and deep infections) in prospective studies with at least a one-year follow-up. The study by Rogmark *et al.* (17) is not included as the result after THR was not reported separately.

**Table 4.** Hip complications and mortality in displaced femoral neck fractures treated with primary THR. Only prospective studies with at least a one-year follow-up are included.

First author	Year	Age, mean	n (f/u)*	Dislocation (%)	Infection (%)	Approach	Mortality (%)
Skinner	1988	81	89 (1)	13	0	Post-lat	23
Jónsson	1996	80	23 (2)	9	0	Troch-ost	13
Johansson	2000	84	50 (2)	22	0	Post-lat	32
Neander	2000	78	43 (4)	14	0	Post-lat	19
Ravikumar	2000	81	89 (13)	20	2	Post-lat	81

\* Follow-up time in years within brackets.

Post-lat = posterolateral. Ant-lat = anterolateral. Troch-ost = trochanteric osteotomy.

In the study by Johansson *et al.* (16), the dislocation rate was correlated with mental dysfunction and the dislocation rate was 32% in patients with mental dysfunction compared with 12% in lucid patients. The lowest dislocation rate was reported by Jónsson *et al.* (23) using a trochanteric osteotomy approach. None of the prospective studies used the anterolateral approach although there are some data indicating that this approach might give fewer dislocations (44, 45).

In a meta-analysis (20), the median number of dislocations in primary THR was 11% (95% CI 0-18) and no significant difference between surgical approaches could be shown, although the short-term mortality was lower in patients operated on using the anterior approach. The median number of deep infections was 1 % (95% CI 0-3).

### **Studies comparing IF and THR**

In prospective randomised studies comparing IF and THR (16, 23), including the study by Neander *et al.* which is partly randomised and partly allocated (24), the number of reoperations is reduced in the THR group compared with the IF group. However, in the study by Johansson *et al.* (16), this difference was almost levelled out due to the large number of dislocations. The functional outcome is generally better in the THR group, but an analysis comparing patients with uneventful outcomes in both groups is lacking, i.e., how does a THR compare with an uneventfully healed femoral neck fracture at the two-year follow-up? In addition, none of these studies evaluates the quality of life. The conclusion drawn from these studies is that THR should be used as a selective primary treatment for relatively healthy elderly patients without mental dysfunction.

### **Studies comparing THR and hemiarthroplasty**

Hemiarthroplasty has been used for a long time in the treatment of femoral neck fractures. Several designs have been used but the main groups are unipolar, where the head of the prosthesis articulates directly with the acetabulum, and bipolar, where an articulating joint is included in order to reduce acetabular wear. Both can be used with or without bone cement. Most unipolar prostheses are of older design and the most frequently used ones are still the Moore (46) and the Thompson prostheses (47), two vintage models from the 1950s.

The bipolar prostheses are gaining increasing popularity in the treatment of femoral neck fractures perhaps due to the theoretical advantages of a reduced risk of acetabular wear. There are a number of stem designs, e.g., older ones like the Thompson bipolar and more modern ones like the Charnley-Hastings design, which combines a relatively modern stem design for cemented use with a bipolar head. There are also systems using a modular cemented stem like the Exeter Bicentric. Modern stems for press fit fixation are rarely used in this patient group.

There are few well performed randomised trials with an adequate follow-up comparing cemented versus uncemented hemiarthroplasty, unipolar versus bipolar and hemiarthroplasty versus THR. There are some indications that the use of cement in hemiarthroplasty reduces pain, improves walking ability and reduces the need for revision surgery (48), but sufficient data for choosing prosthetic designs are still lacking.

### **Studies comparing IF, THR and hemiarthroplasty**

In a recent multicentre RCT (17), IF was compared with primary hip arthroplasty. 384 patients were randomised to IF or hip arthroplasty (THR or hemiarthroplasty – bipolar or unipolar). The choice of arthroplasty method was made using a score reflecting the patient's age, living conditions, walking ability and mental status (Sernbo score). The overall conclusion was that the arthroplasty group had fewer complications, less pain, and better walking ability than the IF group. The dislocation rate was 8% but, for some reason, only those with more than one dislocation were reported. Unfortunately, the

outcome in the THR group is not reported separately, probably because the inclusion criteria make the arthroplasty groups incomparable. The authors recommend primary arthroplasty for displaced femoral neck fractures in patients over 70. The choice of arthroplasty, hemi- or total, should be based on age, functional demands and mental function. A potential problem regarding generalisability is that mental function was classified as alert or slight confusion and was not based on a validated score on cognitive function and is therefore uncertain.

The good long-term outcome after THR has been confirmed in a recent study (25) on the 13-year follow-up of the same population as in the study by Skinner *et al.* (22). 290 patients, age > 65, with a displaced femoral neck fracture were randomised to IF with a sliding compression screw plate, uncemented Moore hemiarthroplasty or THR. After 13 years there was no difference in mortality. The IF, hemiarthroplasty and THR groups had a revision rate of 33%, 24% and 7%, respectively. The dislocation rates following hemiarthroplasty and THR were 13% and 20%. The average Harris hip scores (100 is optimal) were 62, 55 and 80 for the IF, hemiarthroplasty and THR groups. The conclusion drawn was that THR should be considered in active elderly patients with a displaced femoral neck fracture.

## **NUTRITIONAL ASSESSMENT AND ANABOLIC INTERVENTION**

Several studies have evaluated the effect of nutritional treatment after hip fracture (30, 31, 49-53). The results are not consistent, but most studies show a positive effect on either anthropometric or biochemical indicators (30, 49, 52) or on functional measures (30, 31, 50, 52), whereas some of the previous nutrition intervention studies did not report any major beneficial effects (53). It has been suggested that protein has anabolic effects which differ from those of other nutrients (50). Growth factors, e.g. anabolic steroids, testosterone and growth hormone, have been tested in widely varying clinical conditions and may be beneficial (54-56). For example, nandrolone administered for one year to hip fracture patients reduced the wasting of muscle and bone and improved hip function (57).

## **STATING THE PROBLEM**

A hip fracture, especially a displaced femoral neck fracture, is probably the most devastating consequence of osteoporosis in the increasing elderly population. Health care reforms in many countries, e.g., Sweden, seem to focus on hospital costs with a tendency to rewarding fast and simple surgical procedures and abandoning qualified long-term follow-ups. Revision surgery for healing complications has been replaced by waiting lists, walking aids, household help, sheltered housing and institutional care. The economic system encourages cost-evasive behaviour. This is especially unfortunate for elderly patients who are not as prone to complain as younger generations. It is also a waste of resources as low hospital costs are not synonymous with low costs to society and for the patients.

Comprehensive future treatment guidelines should be based on evidence, necessitating a differentiated approach toward hip fracture patients. The hip fracture population consists of several subpopulations with different health states, differing functional demands and differing expectations for the quality of life. The patient's opinion should be incorporated in the outcome analysis and the quality-of-life data generated after dif-

ferent interventions should also be used in future health economic cost-effectiveness analyses.

The quality of life instruments have not been fully evaluated in hip fracture patients and the quality of life after a femoral neck fracture on a longer time scale has not been reported. Reports on the outcome after a displaced femoral neck fracture comparing THR and IF, including a quality-of-life assessment, are lacking. The influence of the nutritional status on the quality of life in hip fracture patients has not been reported, nor has the effect of anabolic intervention, including a quality-of-life assessment.

## AIMS OF THE STUDIES

To evaluate the EQ-5D as an outcome measure after femoral neck fractures in elderly patients. *(Study I)*

To evaluate the quality of life (EQ-5D) after femoral neck fracture in elderly patients treated with internal fixation. *(Study I)*

To evaluate differences in functional outcome and the quality of life (EQ-5D) between undisplaced and displaced femoral neck fractures in elderly patients treated with internal fixation. *(Study II)*

To evaluate the responsiveness of the EQ-5D and SF-36 instruments, i.e. their ability to capture clinically important changes in elderly patients with a displaced femoral neck fracture. *(Study III)*

To evaluate the outcome regarding hip complications, reoperations, hip function and quality of life (EQ-5D) in elderly patients with displaced femoral neck fractures randomised to internal fixation or total hip replacement. *(Study IV)*

To evaluate the nutritional status and its relation to cognitive and physical function and the quality of life (NHP) in elderly female patients with femoral neck fracture. *(Study V)*

To assess whether nutritional treatment, alone or in combination with the anabolic steroid nandrolone, could positively affect the postoperative course regarding nutritional and functional status and the quality of life (EQ-5D). *(Study VI)*

To assess whether fracture healing complications have an impact on nutritional status. *(Study VI)*

## **PATIENTS**

### **ETHICS**

All studies conformed to the Helsinki Declaration and the protocol was approved by the local Ethics Committee. All patients gave their informed consent before inclusion.

### **STUDIES I & II**

#### **Patients and inclusion criteria**

Ninety patients (66 females, 73%), mean age 80 (SD±7) years, with an acute femoral neck fracture after a fall were included in a prospective study. The inclusion criteria were age > 65, independent living, unhindered walking ability and absence of severe cognitive dysfunction (Short Portable Mental Questionnaire, SPMSQ ≥ 3) (58). Patients with fractures not suitable for internal fixation (IF) were not included. The fractures were classified as undisplaced (Garden I and II) or displaced (Garden III and IV) (59). All fractures were internally fixed with two cannulated screws (IF).

#### **Follow-up**

The patients were followed up at 1 week, at 4 months and after a minimum of 12 (mean 17 months). Sixty-five patients treated with IF were available at the final follow-up (2 had primary arthroplasties), 18 were deceased and 5 were lost to follow-up (*Study I*).

Patients with an uneventfully healing fracture, i.e. no signs of non-union or avascular necrosis, at the final follow-up in *Study I* and those lost to follow-up in *Study I* were scheduled for a follow-up after a minimum of 24 months (mean 26 months). Forty-two patients with an uneventfully healed fracture after IF were analysed (2 had primary arthroplasties), 17 had fracture healing complications, 25 were deceased and 4 were lost to follow-up (*Study II*).

### **STUDIES III & IV**

#### **Patients and inclusion criteria**

One hundred and ten patients (87 females, 79%), mean age 80 (SD±6) years, with an acute displaced femoral neck fracture after a fall were entered in the study. Inclusion criteria: age ≥ 70, absence of severe cognitive dysfunction (SPMSQ ≥ 3), independent living status and independent walking capability. Patients with fractures not suitable for IF were not included. After clearance by an anaesthetist, the patients were randomised (opaque sealed envelope technique) to IF with 2 cannulated screws or to a primary total hip replacement (THR). Two patients with aortic valve stenosis were initially cleared by the anaesthetist for surgery and randomised but, after a more thorough examination, they were considered unfit for a THR and were therefore excluded. One patient developed urosepsis while waiting for surgery and was excluded. Two patients were excluded postoperatively because of diagnosed rheumatoid arthritis, although not affecting the hip joint. Three patients changed their mind after randomisation and refused to participate. Thus 102 patients remained, 53 patients in the IF group and 49 in the THR group.

## Follow-up

The patients were summoned at 4 (mean 4.3), 12 (mean 12.4) and 24 (mean 24.2) months for a clinical and radiographic examination. The 4-month results were analysed regarding the responsiveness for the EQ-5D and SF-36 instruments (*Study III*). At the 4-month follow-up (mean 4.3), 3 patients were deceased and another 4 were lost to follow-up, leaving a total of 95 patients available.

The 4-12-(mean 12.4) and 24-(mean 24.2) month results were analysed regarding hip complications, reoperations, hip function and the quality of life (EQ-5D). At the final follow-up, 84 patients were available, 15 were deceased and 3 were lost to follow-up (*Study IV*).

## STUDIES V & VI

### Patients and inclusion criteria

Forty-two women, mean age 80 (SD±7) years, with a femoral neck fracture treated with IF were entered in a pilot study. All data were obtained during the stay in hospital (*Study V*).

Sixty women, mean age 83 years (SD± 5), with an acute femoral neck fracture were included. The inclusion criteria were age ≥ 70 years, body mass index (BMI) <24 kg/m<sup>2</sup>, absence of severe cognitive dysfunction (SPMSQ ≥ 3), independent living status and independent walking capability. Patients with fractures not suitable for IF were not included. The type of fracture was analysed and recorded as undisplaced or displaced. All patients were treated with IF using two cannulated screws. The patients were randomised by the opaque sealed envelope method to open treatment during 6 months. The first group received a protein-rich formula (Fortimel®, 200-400 ml/day, 20-40 g protein/day), i.e. nutrition (*N*). The second group was prescribed the same formula, but in combination with nandrolone (Deca-Durabol® 25 mg i.m./ every 3 weeks), i.e. combined therapy (*CT*), and the third group received standard treatment, i.e. controls (*C*). One patient in the *CT* group changed her mind after inclusion and was accordingly excluded from follow-up. Two patients died and 5 refused to attend the follow-up, giving a total of 52 out of 59 patients available at the final follow-up (*Study VI*).

## Follow-up

The patients in *Study VI* were re-examined after 6 (mean 6.2) and 12 (mean 12.1) months.

## METHODS

### AGE AND SEX

All patients included were elderly, the inclusion criteria in *Studies I and II* being > 65 years of age, in *Studies III, IV and VI*  $\geq 70$  and finally in *Study V* > 70 years of age. This resulted in a mean age of 80 in *Studies I-V*, which is slightly higher than in most studies on patients with femoral neck fractures (5-17) due to the exclusion of younger and middle-aged patients. The higher age, mean 83, in *Study 6* reflects the inclusion criteria selecting lean /malnourished (BMI <24 kg/m<sup>2</sup>) women with a higher frequency of co-morbidity.

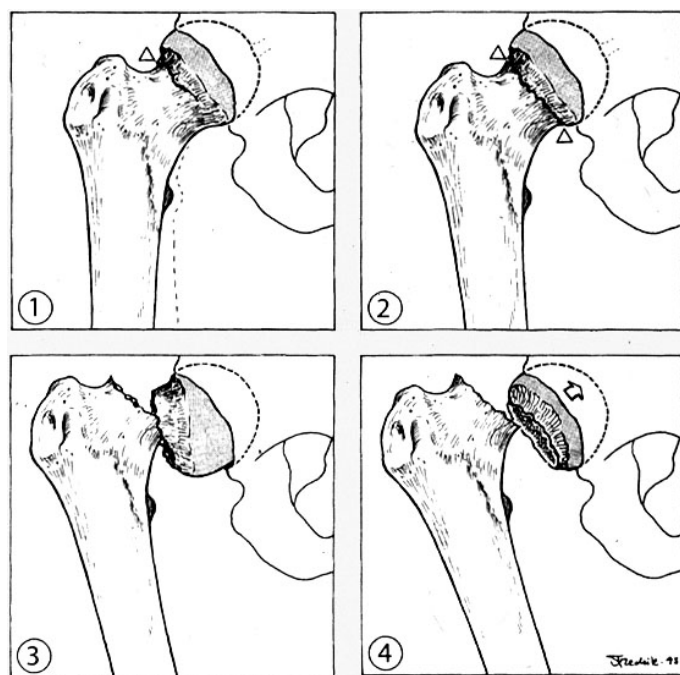
In *Study I-IV*, including both sexes, the proportion of women was 73% (*Studies I and II*) and 79% (*Studies III and IV*). This is also comparable to most other studies on patients with femoral neck fractures in which 75% of the patients are usually females (5-17). In *Studies V and VI*, we chose to include only women as they are most prone to be malnourished among elderly hip fracture patients.

### RANDOMISATION

The randomisation in *Studies III, IV and VI* were performed with numbered, opaque, sealed envelopes.

### FRACTURE CLASSIFICATION

All patients had femoral neck fractures and the fractures were classified as undisplaced



**Figure 1.** Garden's classification.

Ortopedi, U Lindgren, O Svensson ; 2<sup>nd</sup> ed, Liber Stockholm. With the permission of the authors.

(Garden I and II) or displaced (Garden III and IV) according to the Garden classification (4). The classification is based on the displacement in the frontal projection (Charnley's description within brackets).

**Stage I:** valgus impacted fracture (incomplete fracture).

**Stage II:** undisplaced fracture (complete fracture without displacement).

**Stage III:** partially displaced fracture (complete fracture with partial displacement).

**Stage IV:** fully displaced fracture (complete fracture with full displacement) (Figure 1).

The inter-observer variation (60) and the intra-inter-observer variation (61) have

been assessed and showed poor agreement in distinguishing between stage I vs. II and stage III vs. IV. The agreement was acceptable or good (kappa = 0.68) on reducing Garden's system to undisplaced (Stages I and II) and displaced fractures (Stages III and

IV). The breakdown of the fractures into Garden stage III and stage IV does not seem to have any predictive value in determining the quality of the reduction achieved or the incidence of non-union (62). The classification used for dividing the femoral neck fractures into undisplaced (Garden I and II) (Figure 2) and displaced (Garden II and IV) (Figure 3) is by far the most frequently used one and determines the prognosis for fracture healing complications, which differs considerably between the two groups; see Introduction, Surgical intervention, Results after internal fixation.



**Figure 2.** Undisplaced fracture



**Figure 3.** Displaced fracture

## **CO-MORBIDITY**

The Ceder scale (63) categorises the patient as A if she is fully healthy except for the hip fracture and as B if she suffers from another illness not affecting rehabilitation (e.g. hypertension) or as C if she has another illness that affects the rehabilitation (e.g. status after a stroke or Parkinson's disease).

## **ANAESTHESIOLOGICAL ASSESSMENT**

All patients were assessed by the anaesthetist before surgery. In *Studies III and IV*, the assessment included a decision as to whether the patient was fit enough for a total hip replacements (THR). This assessment was always made before randomisation.

## **COGNITIVE FUNCTION**

The SPMSQ (Short Portable Mental Questionnaire) (58) was used to evaluate cognitive function. According to the SPMSQ, patients are classified into four categories: lucid (0-2 errors), mild (3-4 errors), moderate (5-7 errors) or severe (8-10 errors) cognitive impairment. Our inclusion criteria in *Studies I-IV and VI* (three or more correct answers on the ten-item scale) exclude only patients with severe cognitive impairment. In *Study V*, patients with severe cognitive dysfunction were also included, but patients with < 4 correct answers did not participate in the quality-of-life analysis.

## **SOCIAL SITUATION**

In *Studies I-IV and VI*, all patients came from independent living conditions, i.e. they were not institutionalised. Old people's homes and blocks of service flats were re-

garded as an independent living condition. In *Study V*, some patients from nursing homes were also included and the term “sheltered housing” refers to old people’s homes, blocks of service flats and nursing homes.

The need for household help from the community and relatives was assessed in *Studies I-III*, and also the weekly number of hours of help in *Study II*.

## FUNCTIONAL STATUS

### Charnley Hip Score

Charnley’s classification (64) was used to evaluate hip function in *Studies III and IV*. The classification defines the clinical state of the affected hip joint in three dimensions: *Pain* (at the hip), *Movement* (hip motion) and *Walking* (ability to walk). Each dimension is graded from 1 to 6 with 1 = total disability and 6 = normal state (Table 5).

**Table 5.** Charnley’s numerical classification of the clinical state of the affected hip joint.

	<b>Pain</b>	<b>Movement</b>	<b>Walking</b>
<b>1</b>	Severe and spontaneous	0-30°	Few meters or bedridden
<b>2</b>	Severe on attempting to walk, prevents all activity	60°	Time and distance very limited with or without walking aids
<b>3</b>	Tolerable, permitting limited activity	100°	Limited with walking aids, difficult without. Able to stand long periods
<b>4</b>	Only after some activity, disappears quickly with rest	160°	Long distance with walking aids, limited without
<b>5</b>	Slight or intermittent, pain on starting to walk but getting less with normal activity	210°	No walking aids, walks with a limp
<b>6</b>	No pain	260°	Normal

The original presentation of the score was used in *Study IV*. In *Study III*, only the values of the pain score were used and, in order to facilitate understanding, they were presented inverted (0-5), i.e. the value 6 (no pain) was given the value of 0 and accordingly value 1 (severe and spontaneous pain) was given the value 5 and so on.

Although the Charnley hip score is an ordinal variable, the values were presented as mean values and the same approach was used by Charnley (64). In order to make the presentation more complete, the percentage of patients with the best scores, 5 and 6, in each dimension is also displayed (*Study IV*).

### Pain, VAS

In *Studies I and II*, pain while walking was assessed on a visual analogue scale (VAS 0-100 mm, 0 = no pain) and scores over 30 mm were regarded as substantial pain (65).

## **Mobility**

In *Studies I-IV and VI*, all patients had unhindered walking ability preoperatively (i.e. being able to walk either independently or with a walking device). In *Study V* some non-ambulatory patients were also included. In the outcome analysis, the need for walking aids was dichotomised: with or without a walking aid (*Study I*), no walking aid or just one stick versus more than one stick (*Studies II, III and V*). In *Study IV*, the Walking dimension from the Charnely Hip Score was used (Table 5).

In *Study II*, the walking ability was also assessed by a functional mobility test, "Up & Go": the time it takes to rise from an armchair, walk 6 meters and then sit down again (66) and the patients also rated their walking ability compared to before the fracture as unchanged or worse.

## **ADL**

The activities of daily living (ADL) status was assessed according to Katz (67). The Katz index is based on an evaluation of the functional independence or dependence of patients in bathing, dressing, going to the toilet, transferring, continence and feeding. ADL index A indicates independence in all six functions, index B independence in all but one of the six functions. Indexes C-G indicate dependence in bathing and at least one more function.

## **Handgrip strength (HGS)**

In *Studies V and VI*, muscle function was determined from handgrip strength (HGS, Harpenden Hand Grip Dynamometer) (68). Three consecutive measurements were done in the dominant hand and the mean value was calculated.

## **NUTRITIONAL STATUS**

### **Anthropometric assessment**

Body mass index (BMI) (*Study V and VI*) was calculated according to the formula weight (kg) / height (m)<sup>2</sup>. The patients were weighed on the first postoperative day (sitting) and their heel-skull height was measured while stretched in a supine position. In order to test the reliability of supine measurements of height, we compared such registrations of height with standing height (6 months postoperatively) in a similar group of 19 patients with a hip fracture. These two measurements correlated significantly at a high level ( $r=0.94$ ,  $p<0.001$ ) (*Study V*). The weight measurements at follow-up utilised the same equipment (*Study VI*).

Arm muscle circumference (AMC) (*Studies V and VI*) is an estimate of muscle mass and was calculated from the mid arm circumference (MAC) and triceps skinfold thickness (TSF) according to the formula:  $AMC \text{ in cm} = MAC - 0.1 (\pi \times TSF)$  (69). Three consecutive measurements of AMC were done and the mean value was calculated.

The TSF (*Studies V and VI*) is an estimate of fat tissue and was measured with Harpenden® callipers (69). Three consecutive measurements of TSF were done and the mean value was calculated.

## Biochemical tests

Insulin-like growth factor-1 (IGF-1), a peripheral mediator of growth hormone, has anabolic properties (70) and nutrition is a main denominator of IGF-1 activity (*Studies V and VI*). Serum concentrations of the anabolic hormone IGF-1 were determined by RIA after serum had been acid-ethanol-extracted and cryoprecipitated (71). The reference range (i.e.  $\pm 2$  SD) for IGF-1 is 75-180  $\mu\text{g/l}$  for subjects 75 years and older as determined in a reference population (72).

Serum levels of IGFBP-1 were determined according to Povoia *et al.* (73) (*Studies V and VI*). Serum levels of IGFBP-1 are inversely correlated with free IGF-1 (74).

A decreased ratio between IGF-1 and IGFBP-1 has been suggested as a possible biochemical marker for malnutrition (75). A IGF1/IGFBP-1 ratio of  $< 5$  was chosen to indicate a catabolic state (*Studies V and VI*).

Inflammatory status was assessed by C-reactive protein (CRP) according to the routine method of the chemist laboratory of the hospital, i.e. on Hitachi equipment using reagents from Boehringer-Mannheim, Mannheim, Germany, reference value  $< 10$  mg/l (*Studies V and VI*).

## Dual X-ray absorptiometry (DXA)

Dual energy X-ray absorptiometry (DXA, Lunar DPX-L) (76) was used to assess body composition, i.e. fat mass and lean body mass (*Study VI*). This technique exploits the different tissues' varying attenuation of transmitted photons of two different energies and is measured via non-invasive total body scanning.

## Varia

Appetite was assessed in *Study V* and recorded as normal, partly disturbed and severely disturbed and whether the status of the teeth affected food intake or not.

The patients were also asked to evaluate their mood according to a 7-point scale ranging from -3 (very sad all the time) to +3 (very happy all the time) (77).

## QUALITY OF LIFE

The quality-of-life instruments used in these studies were the EuroQol (EQ-5D) (*Studies I-IV and VI*), the Short-Form 36 (SF-36, Swedish acute version) (*Study III*) and the Nottingham Health Profile (NHP) (*Study V*). They are all self-administered and were handed to the patients during their hospital stay and sent to them a couple of weeks before the scheduled follow-up.

## EuroQol (EQ-5D)

The EuroQol (18) is a standardised non-disease-specific instrument (utility measure) for describing and evaluating the quality of life. The EuroQol consists of four components, the first two of which, the health status part (EQ-5D) and the visual analogue scale (EQ-VAS), are used for data collection. The last two, the valuation part and the background data, are designed for valuation of the different states of health.

The first part, the health status profile, EQ-5D, was used in *Studies I-IV and VI*. The EQ-5D has five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension is divided into three degrees of severity: no problem, some problems and major problems. The EQ-5D has been used in several clinical

trials in different fields of medicine (78-81), including hip fracture patients (37), and has been found to have acceptable reliability and validity.

The second part is a 20-cm visual analogue scale, the EQ-VAS, on which the respondent is asked to mark his or her own current state of health on a thermometer-like line calibrated from 0 to 100. The EQ-VAS was used in *Studies I and II* and our experience was that it was difficult for elderly patients to understand it and the response rate for the EQ-VAS was lower (78-91%) compared to the EQ-5D (89-100%) (unpublished data).

The third and fourth parts of the EQ are designed for valuing the 245 ( $3^5+2$ ) possible states (for completeness, “unconscious” and “dead” have been added) for the specified populations. Dolan et al. (82) used the Time Trade-Off (TTO) method to rate these different states of health in a large UK population (UK EQ-5D Index Tariff). We used the preference scores (EQ-5D<sub>index</sub> scores) generated from this population when calculating the scores for our study population. A value of 0.00 indicated worst possible state (dead or a health state worse than dead) and a value of 1.00 indicated best possible state (full health). This is a divergence from the UK EQ-5D Index Tariff where some health states were given a negative score. The appropriate scaling of negative scores is controversial (83) and the same approach was used when generating the values for an age-matched Swedish reference population(84). In order to evaluate recall bias, the rated prefracture EQ-5D<sub>index</sub> scores were compared to the scores of an age-matched Swedish reference population (84) in *Studies I, III, IV and VI*.

### **Short form 36 (SF-36)**

The SF-36 (33, 34) is a quality of life rating instrument (generic measure) comprising 36 statements concerning physical and mental dysfunction. The SF-36 has been widely used and its validity and reliability have been shown to be acceptable in a Swedish population (85). The results for 35 of the 36 questions are aggregated into 8 subscores, i.e. Physical Functioning, Role limitations due to Physical function, Bodily Pain, General Health, Vitality, Social Functioning, Role limitations due to Emotional problems and Mental Health. The raw values of the 8 subscores are transformed and the final subscores for each category range from 0 to 100 (optimal). In *Study III*, an overall (global) SF-36 score was calculated by summing the eight dimensions and dividing by 8. We chose not to use question no.2, Health Transition (the HT item), from the global score since this dimension is a single item ranging from 1 to 5, whereas the other eight dimensions constitute multi-item scales in the 1-100 range. Our intention was to create a global measure of the quality of life even though the clinical importance of each of the eight dimensions probably differs for different individuals (86). A similar approach, although not recommended by the developers, has been used in other clinical studies (86-88). Another approach, not used in this study, is to construct two summaries, Physical (PCS) and Mental (MSC) Component (89). The reason for not using that approach was that the aim of the study was to evaluate the responsiveness of the global scores (EQ-5D and SF-36) and some of the subscores (SF-36 Physical Functioning and Bodily Pain) relevant to hip fracture patients.

## Nottingham Health Profile (NHP)

The NHP is a two-part questionnaire (35) (generic measure). Part I, which was used in *Study V*, consists of 38 questions and measures discomfort or distress in six areas of daily life, namely, lack of energy, pain, emotional reaction, sleep disturbance, social isolation and physical mobility. The answer to each question is given a certain number of points, inversely related to the quality of life, according to a predetermined scale (90). After summing up the points for the answers, a score from 0 (no problem) up to 100 (worst possible) is obtained in each of the six areas. An overall score, although not recommended by the inventors, was calculated from the sum of the scores divided by 6. The same approach has been used by others (87), including the developers of the Swedish version (91). The NHP has been widely used, e.g. to characterise the quality of life of patients with arthritis of the hip joint (92) and myocardial infarction (90) and has been shown to have high validity and reliability (93, 94).

## Recall bias

In the quality-of-life analysis (*Studies I, III, IV and VI*), we chose to compare the follow-up data with the preinjury data as assessed by the patients 1-2 days after the injury had occurred. The patients' ability to correctly recall their quality of life before the hip fracture may be questioned. However, as it is almost impossible to prospectively collect quality of life baseline data for a specific injury population, the alternative methods often used are preinjury recall, as in this and other trauma studies (95), and / or the use of population values. The rated prefracture EQ-5D<sub>index</sub> scores of our patients were compared with the values of an age-matched Swedish reference population (84) (Table 6). The reason why this was not done in *Study II* was that the data on the reference population had neither been published nor was available at that time but, on the other hand, the study population in *Studies I and II* are the same. The study population in *Study V* was also compared with an age and sex-matched reference population (91).

**Table 6.** EQ-5D<sub>index</sub> scores for an age-matched Swedish reference population (84).

Age (years)	EQ-5D <sub>index</sub> scores		
	60-69 (n=387)	70-79 (n=338)	80-88 (n=122)
Total	0.80	0.79	0.74
Male	0.83	0.81	0.74
Female	0.78	0.78	0.74

The rated prefracture EQ-5D<sub>index</sub> score in *Studies I and II* was 0.78, thus showing good correspondence with the reference population. In *Studies III and IV*, the EQ-5D<sub>index</sub> score was 0.83, reflecting the fact that the inclusion criteria probably selected a slightly healthier population, although this is not reflected by the Ceder scale. In *Studies I and II*, the proportion of Ceder A&B was 84% and in *Studies III and IV*, 83%. In *Study VI*, the EQ-5D<sub>index</sub> score was 0.73, thus reflecting the higher inclusion age and the higher frequency of co-morbidity, Ceder A&B was 73%.

## Responsiveness, external criterion (EC)

Responsiveness is defined as the ability of an outcome instrument to detect clinically important changes in a specific condition. The responsiveness of the EuroQol (EQ-5D) and Short-Form 36 (SF-36) instruments was evaluated (*Study III*). Responsiveness was measured in terms of the ability of the EQ-5D and the SF-36 to detect clinically relevant differences in the study population according to an external criterion (EC) based on pain and walking ability. Furthermore, in patients with a less good outcome at 4 months according to the EC, three ways of expressing responsiveness were reported: observed change, standardised effect size (SES) and standardised response mean (SRM) (see Statistical Methods). Besides responsiveness statistics for the EQ-5D and the SF-36 global score, calculations were performed for the SF-36 subscores Bodily Pain and Physical Functioning as, in earlier studies on patients with hip disorders, these subscores have demonstrated high responsiveness (88, 96).

## SURGICAL PROCEDURES

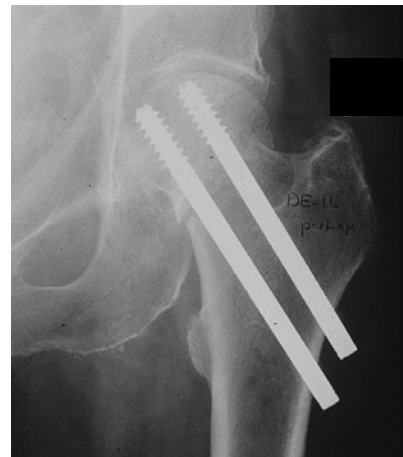
### Internal fixation (IF)

Internal fixation (Figure 4) was carried out with the patient on a fracture table. The fractures were reduced by closed methods with the aid of an image intensifier, reduced to neutral or slight valgus impaction and internally fixed with two cannulated screws (Olmed®). The goals for screw positioning were modified from the recommendations by Lindequist *et al* (15).

In *Studies I and II*, 28 different surgeons, 15 of whom were senior consultants, performed the operations (range 1-14 operations per surgeon). In *Studies III and IV* all primary operations in both groups were performed by either one of two surgeons (JT or HT), both general orthopaedic surgeons specialised in orthopaedic trauma surgery and experienced in both procedures. In

*Study VI*, there were no designated surgeons and the number of surgeons involved was not recorded.

In *Study IV*, the reduction was categorised as good (displacement < 2 mm, Garden angle 160 -175°, posterior angulation <10°), fair (displacement <5 mm, Garden angle 160 -175°, posterior angulation <20°) or poor (displacement > 5 mm, Garden angle < 160° or > 175°, posterior angulation >20°). The screw position was categorised as good if the screw tips were less than 5 mm from the subchondral bone. In the AP projection, the distal screw was intended to be introduced at the level of the lesser trochanter and to lie on the calcar femorale. The proximal screw was introduced at least 2 cm from and parallel to the distal one (the angle being less than 10°). In the lateral projection, the screws were to be parallel and positioned in the central or posterior third of the femoral head and neck.

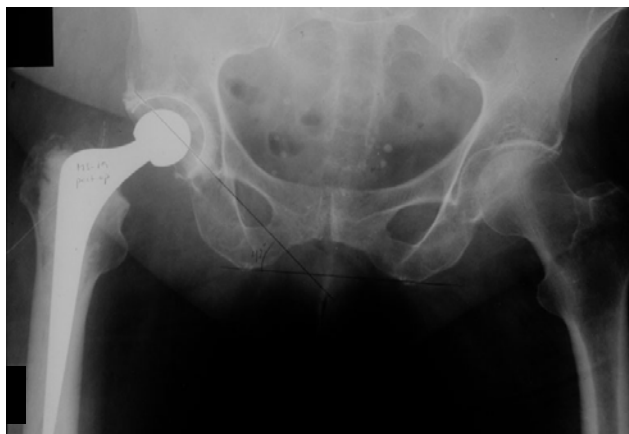


**Figure 4.** Internal fixation of displaced femoral neck fracture.

The fracture was defined as healed if there were visible trabeculae across the fracture line and no signs of avascular necrosis (AVN). Non-union was defined as an absence of radiographically visible trabeculae across the fracture line, including early re-displacement or progressive displacement. AVN was defined as the presence of a subchondral fracture (crescent line), loss of sphericity of the femoral head or segmental collapse.

### **Total hip replacement (THR)**

Total hip replacement (Figure 5) was carried out using an antero-lateral approach, a modified Hardinge approach (97), with the patient in the lateral decubitus position. The implant used was the Exeter®-stem (modular) with a 28-mm head and the OGEE® acetabular component. The stem position was categorised as good if it was in the neutral ( $< 5^\circ$  of varus) position or slight valgus. The cup was considered to be in good position if the lateral opening in the AP view was  $30\text{-}50^\circ$  and if the anteversion in the lateral view was  $0\text{-}30^\circ$ . Limb length was also assessed on the radiographs.



**Figure 5.** Total hip replacement of a displaced femoral neck fracture.

Hip complications such as dislocation and infection were recorded and the follow-up radiographs were analysed for signs of loosening of the femoral (98) or acetabular (99) components.

### **Prophylactics**

Patients were given low-molecular-weight heparin (Fragmin®) preoperatively and for approximately 10 days postoperatively.

Cefuroxim (Zinacef®), 1.5 g, was given preoperatively, followed by two additional doses during the first 24 hours in the THR group in *Studies III and IV*. No prophylactics against infection were given to patients treated with internal fixation.

### **Postoperative rehabilitation**

Patients were mobilised with full weight bearing as tolerated. The patients in the THR group were informed about mobilisation techniques. They were allowed to sit on a high chair immediately after surgery and to abandon the crutches at their convenience. After 6 weeks there were no restrictions.

### **General complications**

General complications up to the 4-month follow-up were recorded.

## STATISTICAL METHODS

The statistical software used was SPSS 10.1 (*Studies II and V*) and 11.0 (*Studies I, III, IV and VI*) for Windows. Differences between distributions were tested by the Chi-square test or Fisher's exact test in all studies.

The approach regarding parametric or non-parametric tests for differences between groups differs somewhat between studies mainly due to varying journal policies. In *Study I*, differences between groups were tested by the Mann-Whitney U-test for independent groups. Differences between more than two groups were tested by the one-way ANOVA and, when significant, were tested in pairs by Gabriel's test. All tests were two-sided. In *Study II*, differences between groups were tested by Student's two-tailed t-test for independent groups. The Wilcoxon signed rank test was used when comparing data at baseline and at follow-up. All tests were two-sided. In *Study III*, differences between groups were tested by the Mann-Whitney U-test for independent groups. Spearman's rho was used as a measure of the correlation between variables. A Wilcoxon signed ranks test was used to compare scores between follow-up and baseline. All tests were two-sided. In *Study IV*, all scale variables were tested for normality with the Kolmogorov-Smirnov test. Student's t-test was used for parametric scale variables in independent groups. The Mann-Whitney U-test was used for non-parametric scale variables and ordinal variables in independent groups. All tests were two-sided. In *Study V*, differences between groups were tested by Student's t-test or the Mann-Whitney U-test for independent groups. Correlations between variables were tested using Spearman's rho. All tests were two-sided. In *Study VI*, all scale variables were tested for normality with the Kolmogorov-Smirnov test. Student's t-test and ANOVA were used for parametric scale variables in independent groups. For non-parametric scale variables and ordinal variables in independent groups, the Mann-Whitney U-test and the Kruskal-Wallis test were used. For comparisons between different follow-up occasions, the paired sample t-test was used in parametric scale variables and the Wilcoxon signed rank test in non-parametric scale variables and ordinal variables. All tests were two-sided.

The use of a parametric or non-parametric test is debatable (100). The most appropriate method is probably the one used in *Studies IV and VI* where all scale variables were tested for normality with the Kolmogorov-Smirnov test and the statistical method was chosen thereafter. The quality of life data should be considered to be ordinal data, except perhaps for the EQ-5D<sub>index</sub> scores, which are preference-based and therefore can be regarded as a scale variable. On the other hand, the EQ-5D<sub>index</sub> scores did not have a parametric distribution in any of the studies and therefore should preferably be tested with a non-parametric test. The statistic approach in *Study II* (Student's two-tailed t-test for independent groups) could therefore be criticised. We have subsequently recalculated the statistics using the Mann-Whitney U-test and the results regarding significance remained unchanged.

In *Study III* the responsiveness statistics included change scores, standardised effect size (SES) and the standardised response mean (SRM). **Change score:** the observed change mean (prefracture - 4-months). The change score is a measure of the extent to which the instrument measures clinical change experienced by the patients. **Standardised effect size (SES):** the observed change divided by the standard deviation of the baseline score (prefracture). The SES provides a standardised measure for the change scores of an instrument so as to allow comparisons between instruments. The SES can

be considered large ( $>0.8$ ), moderate ( $0.5-0.8$ ) or small ( $<0.5$ ) (96, 101, 102). **Standardised response mean (SRM)**: the observed change divided by the standard deviation of the observed change. The SRM also provides a measure for comparing instruments, but the construct makes it less sensitive for sampling sizes than the SES. The SRM is regarded as large ( $>0.8$ ), moderate ( $0.5-0.8$ ) or small ( $<0.5$ ) (87, 96, 101).

In *Study VI*, a logistic regression analyses was performed in order to evaluate factors of importance for change in the quality of life. The model was tested by the Hosmer and Lemeshow goodness-of-fit ( $p=0.92$ ) and was also tested for interactions.

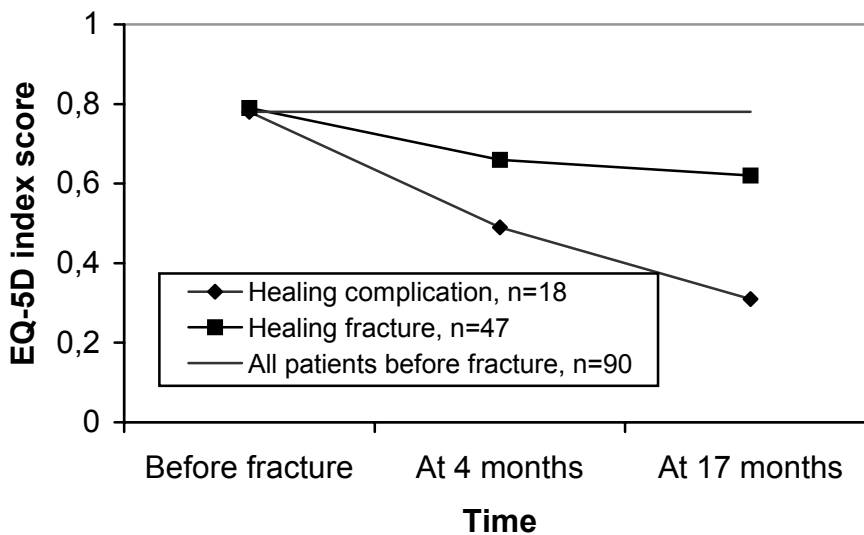
The results were considered significant at  $p < 0.05$ . Trend values were displayed in *Study IV* ( $0.05 \geq p < 0.1$ ) and *Studies V and VI* ( $0.05 \geq p \leq 0.2$ ); all other values are reported as not significant (ns).

## RESULTS

### STUDY I

In 47 of the 65 patients (72%), the fracture was healing and 18 (28%) had a fracture healing complication. There was a substantial decrease in the quality of life according to EQ-5D for all patients after the hip fracture compared to before the fracture. At each follow-up assessment, the mean quality of life (EQ-5D<sub>index</sub> score) was higher for those with healing fractures than for those with fracture healing complications: at 4 months, 0.66 and 0.49 ( $p < 0.05$ ) and at 17 months, 0.62 and 0.31 ( $p < 0.005$ ) (Figure 6).

**Figure 6.** Quality of life (EQ-5D) before fracture and on different follow-up occasions in patients completing the 17-month follow-up ( $n=65$ ) comparing patients with healing fractures and patients with fracture healing complications.



Patients with a pain rating of 30 mm or less on the VAS had significantly better EQ-5D<sub>index</sub> scores than those with a rating of more than 30 mm at both 4 months ( $p < 0.005$ ) and 17 months ( $p < 0.001$ ). Patients with good mobility had significantly better EQ-5D<sub>index</sub> scores than those with poorer mobility at both 4 months ( $p < 0.001$ ) and 17 months ( $p < 0.001$ ). Patients with high-level independence in ADL had significantly better EQ-5D<sub>index</sub> scores than those who were more dependent at both 4 months ( $p < 0.001$ ) and 17 months ( $p < 0.005$ ).

The EQ 5-D Pain dimension correlated significantly with the pain ratings on the VAS scale both at 4 months ( $p < 0.005$ ) and at 17 months ( $p < 0.001$ ). The EQ-5D Mobility dimension correlated significantly with mobility as measured by need for walking aids at 4 months ( $p < 0.01$ ) and at 17 months ( $p < 0.05$ ). The EQ-5D Self-care dimension correlated significantly with the ADL status according to Katz both at 4 months ( $p < 0.001$ ) and at 17 months ( $p < 0.001$ ).

The number of patients capable of answering the EQ-5D 5 questionnaire was high. In the study group, the figures were 100% at inclusion, 97% at 4 months and 89% at 17 months. The decreasing numbers were mainly due to deteriorating cognitive function.

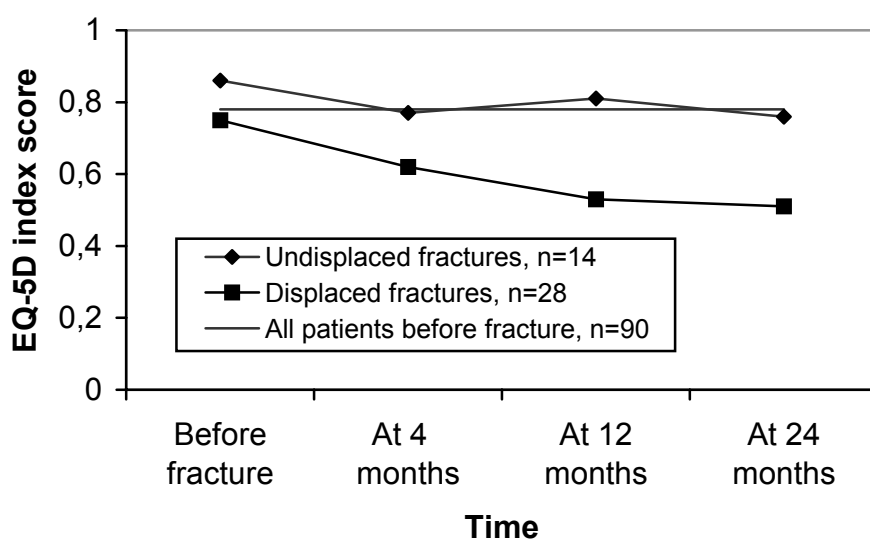
## STUDY II

In patients available at the 24-month follow-up (n=59), the number of fracture healing complications was larger in those with displaced fractures (36%) than in those with undisplaced fractures (7%) ( $p<0.05$ ). The total number of arthroplasty was also larger in patients with displaced fractures. Seventy-six percent of patients with healing complications needed an arthroplasty within 24 months.

The functional status of patients with healed fractures at 24 months favoured those with undisplaced fractures.

The EQ-5D<sub>index</sub> scores for patients, with healed fractures at 24 months, at different stages during the rehabilitation period are shown in Figure 7.

**Figure 7.** Quality of life (EQ-5D) before fracture and on different follow-up occasions in patients with healed fractures at the final 24-month follow-up (n=42).



Patients with primary displaced fractures had significantly lower EQ-5D<sub>index</sub> scores than those with undisplaced fractures at both 12 ( $p<0.005$ ) and 24 months ( $p<0.005$ ). Among the patients with healed undisplaced fractures, there were no significant differences between EQ-5D<sub>index</sub> scores before the fracture and at follow-up. The EQ-5D<sub>index</sub> scores for patients with healed displaced fractures were lower on each follow-up occasion (4 months,  $p<0,05$ , 12 months,  $p<0.005$  and 24 months,  $p<0.005$ ) compared with EQ-5D<sub>index</sub> scores prior to the fracture.

## STUDY III

According to the external criterion (EC), a total of 50 patients (53%) had a good early clinical outcome and 45 patients (47%) had a less good early clinical outcome. Thirty-four patients (71%) in the THR group and 16 patients (34%) in the IF group had a good early clinical outcome ( $p<0.001$ ).

The relationship between EC (good or less good early clinical outcome) and the EQ-5D<sub>index</sub> score and the SF-36 global score showed a significant difference in both comparisons. The SF-36 subscores in relation to the EC showed significant differences in

all dimensions except Role limitations due to Emotional problems. The EQ-5D subdimension scores in relation to the EC showed significant differences in all dimensions.

The standardised effect size (SES) and standardised response mean (SRM) were large for both the EQ-5D and the SF-36 global, with slightly higher values for the EQ-5D. The SF-36 subscores on Bodily Pain and Physical Functioning were large according to SES and moderate according to SRM (Table 7).

**Table 7.** Responsiveness statistics for EQ-5D, SF-36 global and SF-36 subscores Bodily Pain (BP) and Physical Functioning (PF) for patients with a less good outcome at the 4-month follow-up (n=45).

	<b>Observed change (SD)</b>	<b>p value</b>	<b>SES</b>	<b>SRM</b>
EQ-5D	-0.26 (0.29)	<0.001	1.37	0.90
SF-36 global	-16.0 (19)	<0.001	0.89	0.82
SF-36 BP	-23.0 (34)	<0.001	0.82	0.68
SF-36 PF	-20.0 (26)	<0.001	0.88	0.77

The correlation between the change scores for the SF-36 global score and the EQ-5D<sub>index</sub> score was 0.39 (p<0.001). The correlation of the change scores between the SF-36 subscore scales and the EQ-5D<sub>index</sub> score were in the 0.03 – 0.45 range, with the highest values for Bodily Pain, Vitality and Physical Functioning.

There was a good correlation between the SF-36 global score and the EQ-5D<sub>index</sub> score regarding both the values prior to the hip fracture (r=0.57, p<0.001) and at the 4 month follow-up (r=0.62, p<0.001). All SF-36 subscores correlated well with the EQ-5D<sub>index</sub> score on both occasions (r ranged between 0.20 and 0.61, p<0.05 in all comparisons).

## STUDY IV

**Surgical data.** The reduction was considered good in 46 of 53 (87%) patients and fair in the remaining 7. The screw position was good in 51 of 53 (96%) patients.

The stem position was considered good in 48 of 49 patients (98%). In one patient, the stem was in 8° varus. The acetabular component was in good position in 44 of 49 patients (90%). There was no correlation between reduction/screw position and fracture healing complications, nor between screw position and fracture healing complications. One patient with the acetabular component at 6° of retroversion was revised because of recurrent dislocations.

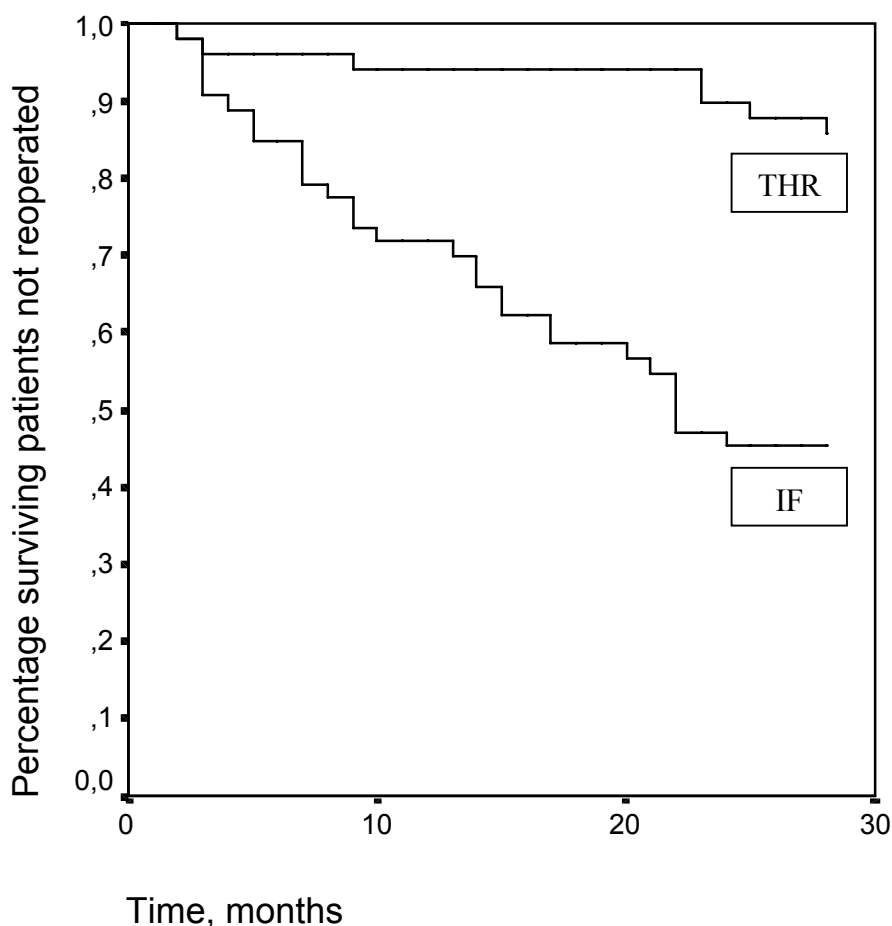
**General complications.** There were no differences between groups regarding general complications. There were no deep infections. Fifteen out of 102 (15%) patients died during the observation period, 10 of 53 (19%) in the IF group and 5 of 49 (10%) in the THR group (ns).

**Surgical outcome.** The rate of hip complications in all patients included in the THR group was 2 out of 49 (4%). The patient with the malpositioned acetabular component sustained three dislocations and was eventually reoperated on 6 months after primary surgery with a revision of the acetabular component and lengthening of the neck of the

prosthesis, whereupon no further dislocation was noted. Another patient sustained, after a new fall 6 weeks postoperatively, a periprosthetic fracture that was successfully treated with internal fixation, and the final outcome was good. There were no signs of radiological loosening of the components in any of the patients at the final follow-up.

In the IF group, 19 of 53 (36%) patients sustained a hip complication (fracture healing complication), 12 of 53 (23%) non-unions and 7 of 53 (13%) AVN. Reoperation was performed on 22 out of 53 (42%) patients. The reoperation was an arthroplasty in 13 of 53 (25%) patients (9 of 53 (17%) THR; 4 of 53 (8%) hemiarthroplasty) and screw removal in 9 of 53 (17%). Three of these complications occurred in patients who later deceased; all three were reoperated on with hip arthroplasty (two THR, and one hemiarthroplasty). Due to local pain, 5 out of 25 (20%) patients with uneventfully healed fractures had their screws removed before the two-year follow-up. The complication rate (hip complications and reoperations) differed between groups ( $p < 0.001$ ). A life table analysis of the surviving patients not having undergone secondary surgery is presented in Figure 8.

**Figure 8.** Life table analysis for all included patients (n=102).



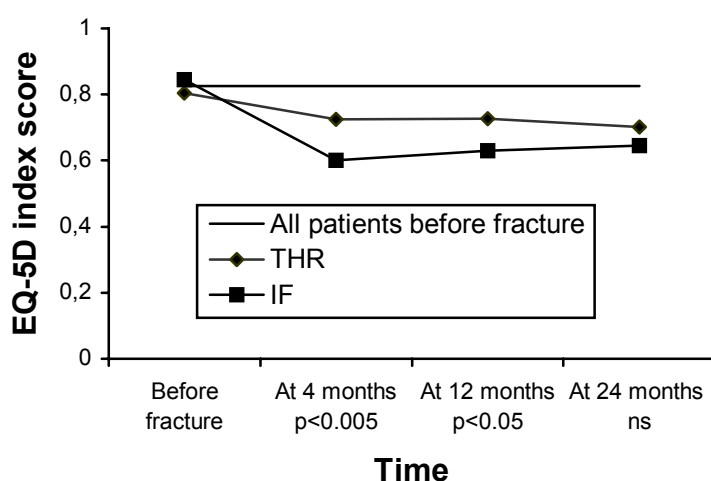
**Outcome and quality of life for all patients.** Generally speaking, hip function was better in the THR group (Table 8). The quality of life (EQ-5D<sub>index</sub> score) was higher in the THR group at each follow-up, but the differences were only significant at 4 and 12 months (Figure 9). The difference in the EQ-5D<sub>index</sub> score, i.e. the change score between inclusion and each follow-up (4, 12 and 24 months, respectively) was calculated. The decline in the EQ-5D<sub>index</sub> score was significantly more pronounced in the IF group between inclusion and all follow-up occasions.

**Table 8.** Hip function according to the Charnley score for all patients available at each follow-up. (4 months, n=95; 12 months, n=92; 24 months, n=84). 1 = total disability, 6 = normal state. Mean values and the percentage of patients with the best scores (5 and 6) in each dimension are displayed.

		THR		IF		p
		Mean	Scores 5 & 6	Mean	Scores 5 & 6	
<b>Pain</b>	4 months	5.7	85%	4.7	55%	<0.001
	12 months	5.3	76%	4.5	50%	<0.005
	24 months	5.6	84%	4.7	54%	<0.005
<b>Movement</b>	4 months	5.0	65%	4.7	49%	ns
	12 months	5.0	70%	4.6	44%	<0.01
	24 months	4.9	67%	4.5	46%	<0.05
<b>Walking</b>	4 months	4.3	33%	3.5	15%	<0.001
	12 months	4.6	50%	3.9	24%	<0.01
	24 months	4.5	51%	3.8	32%	<0.05

p-values given for differences between groups

**Figure 9.** HRQoL for all patients available at each follow-up (before fracture, n=102; 4 months, n=94; 12 months, n=92; and 24 months, n=84). p-values given for differences between groups.



**Outcome and quality of life for patients without hip complications.** At the final follow-up, there remained 25 out of 53 patients (47%) without a hip complication in the IF group and 42 out of 49 (86%) in the THR group. The THR group had significantly better outcomes with regard to pain and walking ability at the 4 and 12-month follow-up (Table 9).

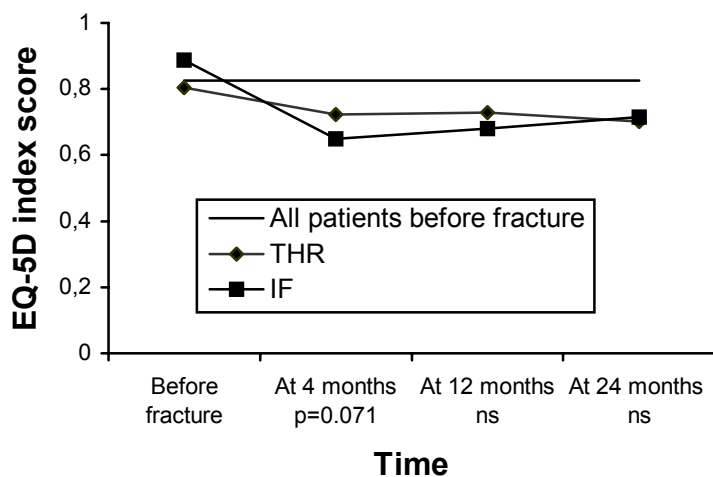
The quality of life did not differ significantly between groups but the decrease in the EQ-5D<sub>index</sub> score was significantly larger in the IF group between inclusion and the 4-month follow-ups (Figure 10).

**Table 9.** Hip function according to the Charnley score for all patients without hip complications at final follow-up (n=67; THR n=42, IF n= 25). 1 = total disability, 6 = normal state. Mean values and the percentage of patients with the best scores (5 & 6) in each dimension are displayed.

		THR		IF		p
		Mean	Scores 5 & 6	Mean	Scores 5 & 6	
<b>Pain</b>	4 months	5.7	88%	5.0	63%	<0,005
	12 months	5.3	76%	4.4	48%	<0,01
	24 months	5.6	83%	5.1	60%	0,062
<b>Movement</b>	4 months	5.0	65%	4.7	55%	ns
	12 months	5.0	68%	4.4	32%	<0.005
	24 months	4.9	68%	4.6	50%	ns
<b>Walking</b>	4 months	4.4	34%	3.8	17%	<0.05
	12 months	4.7	51%	4.0	28%	<0.05
	24 months	4.6	52%	4.3	48%	ns

p-values given for differences between groups

**Figure 10.** HRQoL for all patients without hip complication at final follow-up (n=67; THR n=42, IF n= 25). p values given for differences between groups.



## STUDY V

**Nutritional status.** Twenty patients (52 %) had BMI<21 and 15 (36%) <20. TSF and AMC recordings <10th percentile in a large Swedish reference group were found in respectively 56% and 12% of the study population. Concurrent disabling illnesses were not more prevalent among the underweight subjects (50%) as compared to those with BMI  $\geq$  20 (36%, n.s.).

Serum IGF-1 was lower than 75  $\mu$ g/l in 50% of the cases. BMI correlated positively with IGF-1 ( $r=0.4$ ,  $p<0.05$ ) and negatively with IGFBP-1 ( $r=-0.5$ ,  $p<0.001$ ). Patients with a BMI<20 had significantly lower values for IGF-1 when compared to those with a BMI  $\geq$  20, which was also true of IGFBP-1. Moreover, IGF-1 correlated with AMC ( $r=0.4$ ,  $p<0.05$ ), but not with TSF. IGFBP-1 seemed to inversely correlate with AMC and TSF ( $r=-0.45$ ,  $p<0.005$  and  $-0.3$ ,  $p=0.053$ , respectively). Thirty-two patients (76%) had an IGF-1/IGFBP-1 ratio <5. The ratio was lower among those with BMI < 20 compared to those with BMI  $\geq$  20. Blood samples for CRP analyses were obtained from 25 patients. CRP was elevated, indicating on-going inflammatory activity, in 60% of these patients, but did not differ between patients with a BMI <20 or  $\geq$ 20. However, CRP correlated inversely with IGF-1, i.e.  $r=-0.41$ ,  $p<0.05$ .

**Cognition, functional status and quality of life.** A median value for SPMSQ of 9 indicated an overall good cognitive status. Seven patients (17%) had a SPMSQ score of < 4, evidencing indisputable cognitive dysfunction, 10 (24%) a score of between 4 and 7, and 25 (59%) had a score of  $\geq$  8, denoting a normal cognitive capacity. The SPMSQ score correlated with BMI ( $r=0.44$ ,  $p<0.01$ ), but not with IGF-1 ( $r=0.13$ ) or IGFBP-1 ( $r=-0.21$ ). Possible cognitive dysfunction, i.e. a SPMSQ score < 8, was observed in 69% of those with a BMI < 20, as compared with 24% among those with a BMI  $\geq$  20 ( $p<0.05$ ).

Thirty-one patients (73%) were independent in their ADL according to the Katz index. Patients with a low BMI (<20) tended to be ADL-dependent more often than those with a higher BMI (43% and 19%,  $p=0.095$ ), and they tended to need help at home more often (43% and 19%, respectively,  $p=0.18$ ). Hand grip correlated with BMI ( $r=0.33$ ,  $p<0.05$ ) as well as with AMC ( $r=0.44$ ,  $p<0.01$ ). Furthermore, hand grip was attenuated in patients with a BMI<20. The correlation coefficient for hand grip strength vs. TSF was 0.4 ( $p<0.05$ ) and, for hand grip strength vs. IGF-1 and IGFBP-1, the correlation coefficients were 0.3 ( $p=0.09$ ) and  $-0.34$  ( $p<0.05$ ), respectively.

The Nottingham Health Profile was completed by 30 patients; 5 preferred not to answer the questionnaire and 7 were excluded owing to failing cognitive function (SPMSQ <4). The overall NHP score and the NHP subscores on each of the six quality-of-life areas among the subjects with a BMI<20 and among those with a BMI $\geq$ 20 are shown in Table 10. The table also shows data from an age and sex-matched reference population (91).

The overall score indicated a significantly lower quality of life in the underweight patients. Although all the subscores were worse in the underweight group, only the subscore for lack of energy was significantly different ( $p=0.05$ ) between patients with high and low BMIs.

**Table 10.** Nottingham Health Profile subscores in patients with BMI < 20, BMI ≥ 20 and in an age and sex-matched reference population (91).

Variable	BMI<20 (n = 8)	BMI≥20 (n = 22)	p	Reference population
Lack of energy	57±35.6	25±32.9	0.030	34
Pain	30±21.3	16 ±25.1	0.051	21
Emotional reaction	33±32.6	20±23.0	0.229	14
Sleep disturbance	35±19.8	25±25.1	0.093	32
Social isolation	35±19.8	24±25.1	0.128	10
Physical mobility	37±19.9	29±26.0	0.423	24
Total score	38±19.5	22±19.8	0.045	24

Values are given as means ± SD.

p values are given for differences between groups.

## STUDY VI

**Surgical outcome and complications.** There were no significant differences between groups regarding fracture healing complications and general complications. In the *C* group, there were two deep infections engaging the hip joint. Both of these patients were reoperated on with resection arthroplasty (Girdlestone), and one of them died after seven months. A transient minimal elevation of Se-calcium was noted in six *CT* patients whose condition returned to normal without any changes in therapy. No other adverse drug effects were recorded. In patients with undisplaced fractures completing the 12-month follow-up (n=52), the number of healing complications in patients was 1 out of 20 (5%) and, in patients with displaced fractures, it was 16 of 32 (50%), (p<0.005).

**Nutritional and functional outcome.** At inclusion, the mean BMI was 20.4 (SD 2.3) kg/m<sup>2</sup>. Serum IGF-1 was subnormal in 27 out of 57 (47%) patients. BMI correlated positively with IGF-1 (r=0.4, p<0.005). Fifty-four out of 59 (92%) had an IGF-1/IGFBP-1 ratio of less than 5, indicating a catabolic state.

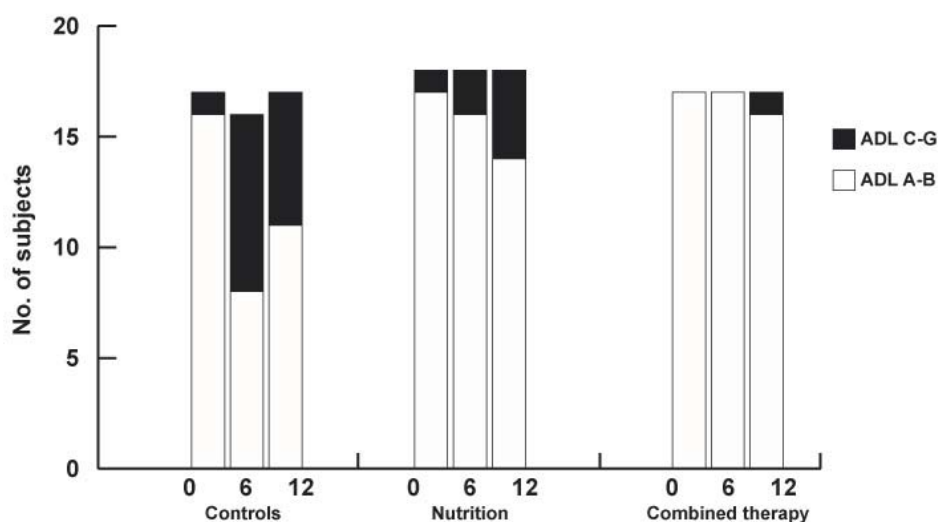
At 6 months, the *C* group displayed significant decreases in weight, TSF, AMC, lean body mass and fat tissue mass. In the *N* group, there was a corresponding decrease in lean body mass while the fat mass appeared to be preserved. The *CT* patients experienced a significant decrease in TSF and fat tissue but maintained their lean body mass. All groups showed an expected decrease in CRP and corresponding increases in se-albumin and se-IGF-1. Differences in lean body mass and se-albumin were significant between groups, in favour of *CT*.

At the 12-month follow-up, i.e. 6 months after cessation of the intervention, the *C* and *N* groups still had reduced lean body mass and the *CT* group had a significantly reduced fat tissue mass. All groups still had a higher IGF-1 than at inclusion and the *N* and *CT* groups had higher se-albumin than at inclusion.

Maintenance of independence in ADL was significantly more common in the *CT* and *N* groups (p<0.005) at the 6-month follow-up as compared to the *C* group and there was a trend towards the same difference at the 12-month follow-up.(Figure 11). The *CT* group also showed a significant increase in HGS, a variation that tended to differ from

that in the other two groups. Mobility was not significantly different between the groups. The median hospital stay during the first year after surgery was 27 (5-197) days in group *C*, 20 (5-356) days in group *N* and 18 (8-51) days in the *CT*-group (ns).

**Figure 11.** ADL according to Katz at inclusion, 6 months and 12 months. Controls (*C*), nutrition group (*N*) and patients on combined therapy (*CT*), i.e. nutrition and nandrolone. *p* value for differences between groups at inclusion (ns), at 6 months ( $p<0.005$ ) and at 12 months ( $p=0.109$ ). Difference between *CT* and *C* at 6 months ( $p<0.005$ ), between *N* and *C* ( $p<0.05$ ) and between *CT* and *N* (ns).

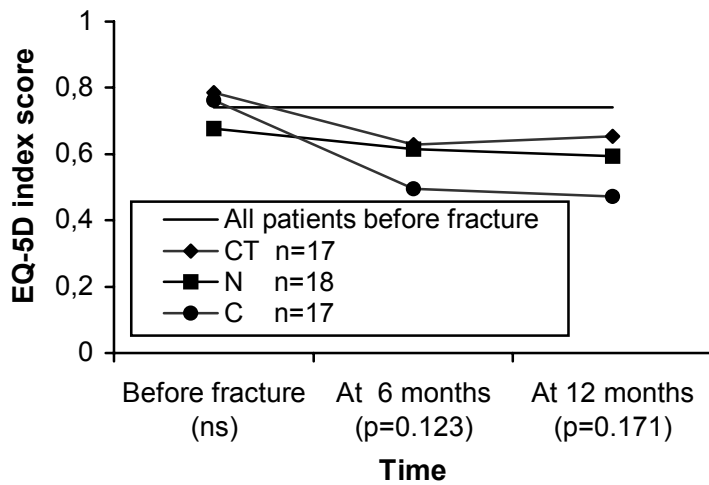


ADL A-B indicates independence in all six functions or independence in all but one. ADL C-G indicates dependence in bathing and at least one more function. One missing value in group *C* at 6 months.

**Quality of life.** There were no significant differences in the quality of life between the groups at the start, but there were trends towards a difference at the 6- and 12 month follow-ups (Figure 12). The EQ-5D<sub>index</sub> score declined significantly in group *C* between inclusion and the 6-month follow-up ( $p<0.005$ ) and the 12-month follow-up ( $p<0.01$ ), while the EQ-5D<sub>index</sub> score did not fall significantly in group *N* at 6 months ( $p=0.077$ ) or at 12 months ( $p=0.118$ ). The EQ-5D<sub>index</sub> score in the *CT* group decreased at 6 months ( $p<0.05$ ), but not at 12 months ( $p=0.092$ ). The decline in EQ-5D<sub>index</sub> score, compared between groups, tended to be more pronounced in group *C* than in groups *N* and *CT* at both 6 months ( $p=0.104$ ) and 12 months ( $p=0.059$ , Kruskal-Wallis test).

Next we performed a logistic regression analysis in order to evaluate factors of importance for changes in the quality of life. A decreased EQ-5D<sub>index</sub> score and an unchanged or improved EQ-5D<sub>index</sub> score were used as dependent variables. Randomisation groups, fracture type, age and BMI were tested as independent variables in the model. The analyses showed that randomisation to the *CT* group was associated with an increased odds ratio for an improved quality of life at the end of the 6-month intervention period ( $p<0.05$ ) along with an undisplaced fracture and old age (>84 years), ( $p<0.005$ ).

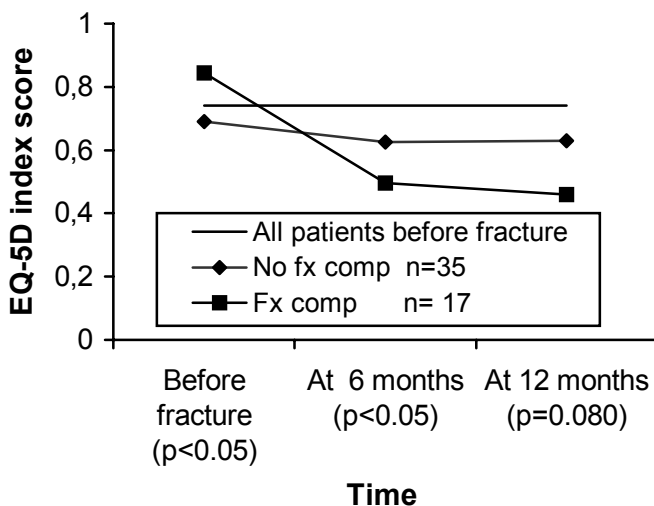
**Figure 12.** Quality of life according to the EQ-5D for all patients completing follow-up (n=52), comparing randomisation groups (C, N and CT). p values are given for differences between groups.



**Fracture healing complications and outcome.** Out of the 52 patients completing the whole follow-up, 17 (33%) developed a fracture healing complication up to the 12-month follow-up. These 17 patients did not differ from the 35 patients without a fracture healing complication regarding background data, except that they rated their prefracture quality of life higher, EQ-5D<sub>index</sub> score  $0.84 \pm 0.14$  vs.  $0.69 \pm 0.25$  ( $p < 0.05$ ), had a lower IGFBP1 at inclusion ( $p < 0.05$ ) and more often had a displaced fracture, 16 out of 17 (94%) ( $p < 0.005$ ).

The decrease in body weight and lean body mass was significantly more pronounced at 6 months in patients with fracture healing complications. The EQ-5D<sub>index</sub> score for the patients developing a fracture healing complication fell from a significantly higher prefracture level to a significantly worse level at 6 months, as compared to patients without a fracture healing complication, and tended to remain lower (Figure 13). The median hospital stay during the first year after surgery was 17 (5-197) days in patients with no fracture healing complication and 31 (5-356) days in patients with a fracture healing complication ( $p < 0.05$ ).

**Figure 13.** Quality of life according to the EQ-5D for all patients completing follow-up (n=52), comparing patients with (*Fx comp*) and without fracture healing complications (*No fx comp*). p values are given for differences between groups.



# GENERAL DISCUSSION

## QUALITY OF LIFE

Does a quality of life assessment add any further dimension to conventional outcome measures in orthopaedic surgery? Fracture healing complications, hip complications, general complications and reoperation rates are hard facts necessary for evaluating surgical procedures. Moreover, specific hip scores such as the Charnley hip score (64) and the Harris hip score (103) give valuable information on hip function. However, these data need to be complemented with outcome measures that gives us information on how the patient rates the outcome and to what extent the injury/disease influences other areas of life, i.e. the quality of life. Otherwise, there is a substantial risk of underestimating or misinterpreting the impact of an injury/illness. The studies in this thesis (*Studies I and III*) evaluates the EQ-5D and the SF-36 in patients with femoral neck fractures and also measures the quality of life on a fairly long-term time scale after different interventions (*Studies I,II,IV and VI*). Evaluation of a quality of life instrument typically involves the comparative evaluation of reliability, validity and responsiveness. The latter two were evaluated in *Studies I and III*.

### Validity

Validity, i.e. how appropriately a questionnaire measures the condition of interest, was evaluated comparing the EQ-5D (EQ-5D<sub>index</sub> scores and subdimensions) with other established outcome measures (construct validity). There was a good correlation between the EQ-5D<sub>index</sub> scores and outcome measures such as mobility, independence in ADL and independent living status. There was also a good correlation between the EQ-5D Pain dimension and pain rated on the VAS scale, between the EQ-5D Mobility dimension and mobility assessed by the need for walking aids and between the EQ-5D Self-care dimension and the degree of dependence in ADL according to Katz, which indicates a high construct validity (*Study I*). The validity was also tested for both the EQ-5D and the SF-36 when the scores of both instruments were analysed in relation to an external criterion (EC) based on pain and impaired walking ability (*Study III*). Patients with a less good outcome according to the EC had significantly lower total SF-36 and EQ-5D<sub>index</sub> scores. The SF-36 subscores were also significantly lower for patients with less good outcomes in all dimensions except Role limitations due to Emotional problems (RE) and there were also significant differences in all of the EQ-5D subdimension scores. This is in accord with previous studies in which the EQ-5D has been shown to compare favourably in terms of internal and external validity with more elaborate quality-of-life instruments (79-81).

### Responsiveness

Responsiveness is defined as the ability of an outcome instrument to detect clinically important changes in a specific condition. A common method of demonstrating responsiveness of a quality-of-life instrument is to compare scores before and after a treatment of known efficacy. When treating and studying injured patients the question is complicated by the fact that the patients' health status before the accident is assessed in retrospect. In order to study responsiveness of the EQ-5D and the SF-36 in patients with hip fractures, we chose to use a randomised patient population with two different surgical

treatment options, i.e. internal fixation (IF) and total hip replacement (THR), after a displaced femoral neck fracture. Responsiveness was measured in terms of the ability of the EQ-5D and the SF-36 to detect clinically relevant differences in the study population according to an external criterion based on pain and walking ability, two important outcome measures after a hip fracture. The 4-month follow-up was chosen because the decline in function and quality of life seems to be most pronounced during the early phase of rehabilitation (39). The responsiveness was quantified by the standardised effect size (SES) and the standardised response mean (SRM). Both the EQ-5D and the SF-36 global score yielded high values, indicating good responsiveness. The values for the SF-36 subscores Bodily Pain and Physical Functioning were large according to SES and moderate according to the SRM, indicating that these subscales also have acceptable responsiveness in hip fracture patients. The SRM should probably be the preferred statistical measure as the SES may be less accurate because it uses the standard deviation of the prefracture score and, accordingly, does not contain information on the accuracy of the instrument in detecting change over time. The ceiling effect shown in previous studies (104) suggests that the EuroQol could be less responsive to changes in conditions with low morbidity. This was not a significant problem in elderly patients with a femoral neck fracture, a condition with major morbidity.

### **Response rate**

The high response rate of the EQ-5D and SF-36 questionnaires in our studies supports the assumption that both instruments are suitable for use in an elderly hip fracture population. Previous studies on the SF-36 have shown a lower completion rate compared to the EuroQol (104), especially in elderly patients (34, 78). The completion rate was not a problem in our studies, perhaps because the inclusion criteria selected relatively healthy elderly patients without severe cognitive dysfunction.

### **Conclusion**

Both the EQ-5D and the SF-36 seem to capture changes in the multifaceted domains of physical, psychological and social functioning after a displaced femoral neck fracture in elderly patients. Based on our findings, we believe that both the EQ-5D and the SF-36 can be used as outcome measures after the treatment of hip fracture patients. In our opinion, quality of life assessments are primarily indicated in groups of patients, clinical trials or for quality improvement in clinical practice. The benefit of such an assessment in an individual patient is limited due to the multifactorial nature of quality of life. The more comprehensive generic measure, the SF-36, gives a more detailed health profile. However, if the main focus is on the global health status, the preferred instrument in elderly patients may be the EQ-5D because of its previously documented higher completion rates and slightly higher responsiveness. In addition, since it is preference-based, the EQ-5D can also be used to construct quality-adjusted-life years (QALYs), which are frequently used in cost-effectiveness analyses.

## **SURGICAL INTERVENTION**

### **Inclusion criteria**

The inclusion criteria need to be assessed to evaluate the generalisability of the results. For several reasons, we studied a rather healthy group of elderly patients (*Studies I-IV*).

Firstly, validating a quality-of-life questionnaire does not allow inclusion of patients with severe cognitive dysfunction. However, the number of patients admitted from independent living circumstances with severe cognitive impairment is limited. In a study by Strömberg *et al.* (105) on 256 hip-fracture patients admitted from independent living circumstances, only 10% were severely cognitively impaired (SPMSQ < 3). Secondly, patients with walking capability from independent living conditions would recognise a substantial decrease in their quality of life on sustaining a fracture complication, which would not be as obvious in an already bedridden and institutionalised patient. Thirdly, only relatively healthy elderly patients with high functional demands and a relatively long life expectancy can fully enjoy the advantages of a THR (*Studies III and IV*). Finally, patients with cognitive dysfunction have been shown to have a high rate of dislocations (16, 20). The lower age level in the randomised surgical trial (*Studies III and IV*) is of course debatable, but considering all factors, such as fracture healing complications after internal fixation (IF), the risk of revision due to aseptic loosening after THR and the expected mean survival in the age group, 70 years of age seems reasonable. On the other hand, we did not set an upper age limit, but the other inclusion criteria excluded the oldest and most fragile patients, i.e. this approach considers biological age rather than chronological age.

In spite of the inclusion criteria, our study populations seem to be comparable to those of other studies on elderly patients with femoral neck fractures with regard to age, sex, fracture type and co-morbidity (5-17).

### **Internal fixation (IF)**

The rate of fracture healing complications after internal fixation (IF) in patients with undisplaced fractures was low and equal to or better than that in most previous studies (5, 7-15). The complication rate among patients with displaced fractures was at the same level or better than that in most previous studies (5-17). But in spite of a good fracture reduction and screw position in the vast majority of patients in *Study IV*, the complication rate was, in our opinion, unacceptably high.

Three studies are often referred to (21) as demonstrating optimal results after a displaced femoral neck fracture treated with internal fixation. 1/ The well-conducted study by Strömqvist *et al.* (13) on 626 patients shows a fracture healing complication rate of 41% among two-year survivors, thereby confirming the high complication rate. 2/ The exceptionally good results from Rehnberg *et al.* (9) reporting only 12% fracture healing complications, all avascular necrosis (AVN), in a study of 44 consecutive patients, 43 of whom had a displaced fracture. These good results from a single surgeon could not be reproduced in an RCT from the same institution using the same implant (106) where the one-year fracture healing complication rate was 21%, compared with 23% in *Study IV*. 3/ The promising one-year results with the Uppsala screw (Olmed®) reported by Olerud *et al.* (107) have not, to our knowledge, been followed-up by a report on the two-year results and therefore could not be fully evaluated. I therefore believe that the results after IF in osteoporotic elderly patients with a displaced femoral neck fracture, i.e. 35-50% fracture healing complications, cannot be significantly improved with current fixation techniques. Thus the old adage “the bad results of nailing are the results of bad nailing” may need to be modified regarding displaced femoral neck fractures.

The consequence of a fracture healing complication is usually a secondary arthroplasty, given an adequate follow-up. If not, there is a risk that these elderly patients will

not return for an orthopaedic consultation and adapt instead to an unnecessarily low function and quality of life. This is probably the situation in many parts of Sweden today where patients with femoral neck fractures are not routinely scheduled for follow-up mainly due to limited health care resources. This is probably not correct from a macro perspective, as the indirect costs are often higher than the direct health care costs.

It is sometimes claimed by individual institutions that they have a significantly better outcome after IF, but these data are nearly always based on retrospective studies or on the reoperation rate. For one thing, orthopaedic surgeons today rarely have the opportunity or desire to follow-up their patients, which may contribute to an overly optimistic outlook on the prognosis. Furthermore, data based on the patient's own ability to return for follow-up will nearly always underestimate the number of fracture healing complications and, accordingly, the need for a secondary arthroplasty.

Arthroplasty after failed IF was performed in 76% of the patients in *Study II* and in 68% of those in *Study IV*. This is a considerably higher frequency than previously reported (7, 13) and could be due to our inclusion criteria, which resulted in the selection of a more lively and independent population with higher functional demands compared with many other studies. Admittedly, the indications for an arthroplasty are nearly always relative and are aimed at improving the patient's function and quality of life and must be balanced against surgical risks. A risk for the elderly patient of a prolonged period with decreased function is that the disability becomes permanent. Owing to acute problems after failed IF, some of the patients were reoperated on by orthopaedic surgeons not involved in the study, which explains the unfortunate mixture of methods in the secondary arthroplasties (THR vs. hemiarthroplasty). Consequently, 24% (*Study II*) and 32% (*Study IV*) of the patients with a diagnosed fracture healing complication were not reoperated on during the study period. There is a substantial risk that some of these patients will develop indications for hip replacement during subsequent follow-ups due to progressive hip disability. To sum up, the reoperation rate after internal fixation does not appear to be a suitable single outcome measure as it incorporates the patients' coping ability, surgeons' differing indications for arthroplasty and the inequality of health care resources. Also, secondary THR after a fracture healing complication appears to yield inferior results regarding hip function than primary THR (24).

There is a strikingly large decrease in the quality of life after a femoral neck fracture and this decrease is, as might be expected, significantly larger among patients with fracture healing complications. But perhaps somewhat surprisingly, patients with uneventfully healed undisplaced fractures have a better outcome regarding quality of life than those with uneventfully healed displaced fractures. Why? One explanation might be the shortening of the femoral neck during healing (108, 109) with altered biomechanics of the hip and prominent screws leading to impaired hip function. Another might be that patients with displaced fractures represent a negative selection, with more severe osteoporosis and poor general health, although the latter is not confirmed in our study (*Study II*). If so, it would not be possible to alter the prognosis with a different surgical intervention, e.g. a THR. Both factors are probably operative.

### **Internal fixation (IF) versus total hip replacement (THR)**

Could this discouraging outcome after IF be altered by treating the patients with a primary THR? The optimal treatment of displaced femoral neck fractures is unsettled. For

many years, the general treatment in Sweden has been IF, mainly based on the argument that retaining the patient's own femoral head will always yield better hip function than an arthroplasty. In most other European countries, the preferred treatment has been a primary arthroplasty, most often a unipolar or bipolar hemiarthroplasty. The majority of studies in the field focus on complications and reoperations, but to a lesser extent on hip function and almost never on an assessment of the quality of life. The population of elderly patients with femoral neck fractures is heterogeneous and comprises a spectrum of patients ranging from the independent, healthy subject with high functional demands to the institutionalised, cognitively impaired and bedridden patient. The currently available techniques (IF, unipolar arthroplasty, bipolar arthroplasty and THR) have different outcome and different risk profiles. We have only studied a healthy subgroup of the entire hip fracture population. Perhaps this heterogeneity among hip fracture patients is one reason why there have been, and still are, such differing opinions? The future strategy probably should be to individualise the treatment based on patient-related factors and not only on fracture type.

In our series of relatively healthy elderly patients with a displaced femoral neck fracture – constituting approximately 30-40% of all patients with femoral neck fractures – a primary THR gave rise to few complications. The 2% dislocation rate after primary THR in this study is unusually low (16, 20, 22, 24). One reason is probably the anterolateral surgical approach (44, 45). In our own experience, this is the best approach for optimising stability, which is the primary goal in patients with femoral neck fractures. Recent RCTs of THR for femoral neck fractures (16, 24) used the dorsolateral approach and reported a dislocation rate of 14% and 22%. Another factor involved in avoiding dislocations was the exclusion of patients with severe cognitive dysfunction. In the series reported by Johansson *et al.* (16), the dislocation rate in patients with mental dysfunction was 32%, compared with 12% in lucid patients. Also, I believe the experience of the surgeons is important. It is often more technically demanding to perform a stable THR on a fracture than in osteoarthritis. A modular prosthesis design allowing the surgeon to optimise the offset during surgery probably also decreased the risk of postoperative dislocations – which is indeed a troublesome complication. Deep infections were not a problem and seem to be rare with the modern technique including adequate antibiotic prophylaxis (16, 23, 24). The cumulated risk of aseptic loosening also seems to be minor in this age group (25, 42).

The general complication rate in *Studies III and IV* was similar in both groups. The overall two-year mortality rate, 15% (*Study IV*), is lower than that in most other studies on internal fixation (5-8, 10-17, 20) and lower than in modern RCTs comparing IF and THR. Johansson *et al.* (16) reported an overall two-year mortality rate of 33%, probably due to a selection of slightly older (mean age, 84) and some cognitively impaired patients (mental dysfunctional in 45%). Neander *et al.* (24) reported an overall mortality rate at the two-year follow-up of 24% and, as in our study, there was a tendency to increased mortality in the IF group (28%) compared with the THR group (19%). Obviously, today the surgical procedure itself does not increase the mortality rate. No patient in the THR group died during the first 4 months post surgery. One reason for the increased mortality rate in the IF group could of course be a selection bias, but this seems less likely as the randomisation groups in our study were comparable regarding baseline data. A more probable explanation is perhaps that the functional deterioration and pain impaired the patient's general condition and thereby increased mortality. Contrary to conventional wisdom, THR is probably a lesser trauma than IF followed by pro-

longed postoperative pain. Deceased patients were four years older and had a lower quality of life than survivors. The number of hip complications in the deceased patients was comparable to that in the entire group, but the number of impending hip complications among early on deceased patients is not known since it may take two years after surgery to detect a healing complication of a femoral neck fracture.

Most hip function scores (64, 103) have been validated for patients with THR after degenerative joint disease, but they have also recently been used in studies comparing THR and IF in patients with femoral neck fractures (16, 24). We used the Charnley hip score (*Studies III and IV*) because it is well validated and the outcome is indicated in three important dimensions regarding hip function, *Pain*, *Walking* and *Movement*. The outcome regarding hip function was generally better in the THR group even when only comparing patients without hip complications in both groups. The explanation of the generally lower values for *Walking* compared to studies on patients with THR (64) after osteoarthritis probably has to do with older age and more frequent co-morbidities in the hip fracture population. Even before the fracture, 22% of the patients used some sort of walking aid for other reasons than hip disorders. The Harris hip score (103) might be a preferred alternative as it includes a valuation of the included dimensions, pain, function and range of motion, where the highest maximum scores are given for pain and function and produce an overall score. Additionally, the function dimension includes, besides walking ability, important daily activities such as climbing stairs and dressing.

The quality of life was better in the THR group than in the IF group on comparing all available patients, significantly so at the 4 and 12-month follow-ups, and the decline in the quality of life was less in the THR group between prefracture and all follow-up occasions. This difference was diminished on comparing only patients with an uneventful postoperative course. The higher complication and mortality rates in the IF group seemed to select a group of patients with a higher quality of life among those with an uneventful postoperative course. In this limited group of patients alive and without hip complications at the two-year follow-up (86% in the THR group and 47% in the IF group), the quality of life was nearly equal at the final follow-up, but the decrease in the quality of life compared with before fracture was larger in the IF group and, significantly so in the early postoperative phase. The decrease in the EQ-5D<sub>index</sub> score after THR was comparable to the decrease after an uneventfully healed undisplaced fracture, i.e. 0.10 (*Study II*).

## Conclusion

The results support and confirm the present policy of IF for undisplaced femoral neck fractures in the elderly. The fracture healing complication rate is low and patients with healed fractures regain the same quality-of-life level as before the fracture. With regard to displaced fractures, our studies confirm the high complication rate in elderly patients treated with internal fixation and, even in uneventfully healed displaced fractures, most patients never regain their prefracture quality-of-life level.

The results also supports the notion that a primary THR is the treatment of choice for an elderly, relatively healthy, lucid patient with a displaced femoral neck fracture. The complication rate after THR is lower than after IF, provided that the surgical procedure is optimised for minimising the number of dislocations, and the outcome regarding hip function and quality of life is generally better. On the other hand, for the group of patients with an uneventfully healed fracture two years after IF, the hip func-

tion and quality of life are comparable to those achieved after a primary THR. Accordingly, IF can be justified only if the follow-up is scrupulous and scheduled at regular intervals with urgent conversion to an arthroplasty if a fracture healing complication is diagnosed. A surgeon who is well experienced in hip arthroplasty should perform the THR, and I believe the anterolateral approach is preferable. The optimal lower age for a THR is yet to be determined, but current results support, in our opinion, at least 70 years of age. The treatment algorithms for patients with displaced femoral neck fractures in the future would benefit from being patient-related rather than diagnosis-related.

## **NUTRITIONAL ASSESSMENT AND ANABOLIC INTERVENTION**

In *Study V*, the often suggested association between malnutrition and femoral neck fractures among the elderly was confirmed. A large proportion of the hip-fracture patients exhibited, apart from reduced muscle mass and subcutaneous fat, subnormal IGF-1 levels. IGF-1 has been reported to be a good marker for nutritional status (110) and, accordingly, IGF-1 correlated with the anthropometric variables. Serum levels of IGFBP-1 are inversely correlated with free IGF-1 (74), which explains the inverse correlations between IGFBP-1 and the anthropometric variables. Recently, the decreased ratio between IGF-1 and IGFBP-1 has been suggested to be another possible biochemical marker for malnutrition (75). In support of this suggestion, we found that the ratio was significantly lower in the underweight subjects than in those with a BMI  $\geq 20$ . Although an osteoporotic hip fracture is generally caused by a low-energy fall, the catabolic stress induced by the fracture itself may have contributed to the observed reduction in serum IGF-1 concentrations.

An interesting finding in *Study V* was the close relationship between nutritional depletion and scores in the NHP, indicating a low quality of life. The differences in quality-of-life ratings were especially evident when the patients were divided into two groups according to BMI (more or less than 20). Among the six areas that were evaluated, the feeling of a lack of energy stood out as significantly reduced in the underweight patients. This might be of specific relevance for hip-fracture elderly patients in whom energy and motivation for rehabilitation are of crucial importance for the prognosis after the fracture.

The frequent occurrence of cognitive dysfunction among the patients raises the question of whether the trauma may have induced confusion or whether the cognitive impairment was manifest before the trauma. The latter hypothesis is supported by several reports on associations between malnutrition and reduced cognitive functions (111, 112). It is conceivable that the combination of malnutrition and cognitive dysfunction contributes to the propensity for falls and subsequent hip fracture as well as that the combination of malnutrition and trauma contributes to the development of confusion and impaired cognitive function.

The results of *Study VI* showed that nutritional support in combination with nandrolone given to lean female patients with femoral neck fractures treated with internal fixation (IF) had a significant positive effect on ADL function, quality of life and lean body mass during an intervention period of 6 months. Moreover, something not previously demonstrated, fracture healing complications had a significant negative impact on nutritional outcome, i.e. weight and lean body mass, apart from more expected negative effects on the quality of life and duration of the hospital stay.

The major finding of positive effects on ADL and the quality of life in patients on combined therapy with nutrition and nandrolone may be due to sustained lean body mass and muscle function, i.e. hand grip strength. At the same time, there were significant decreases in lean body mass and arm muscle circumference (AMC) in group C. The positive effects achieved during the 6-month treatment period were, as expected, not fully retained after the treatment was stopped. Nandrolone administered to hip fracture patients has been evaluated previously in two studies. In one, four weeks of weekly injections had no effect (113). In the other, nandrolone, administered to a mixed population of hip fracture patients every three weeks for one year, resulted in retained muscle volume in the injured leg as compared to the control group (57). Moreover, this study by Hedström *et al.* showed that hip function and gait speed were better in the nandrolone-treated group.

Patients receiving nutritional support alone also retained their ADL function better and showed a lower decrease in the quality of life compared to controls. However, the positive effects on the quality of life noted in the *N* patients may be partly explained by a lower percentage of displaced fractures in this group. This conclusion is indicated by the regression analyses showing that a non-displaced fracture was strongly related to a positive outcome regarding the quality of life. Several studies have evaluated the effect of nutritional treatment after a hip fracture (30, 31, 49-53). The results are not consistent, but the majority of the studies show a positive effect on either anthropometric or biochemical indicators (30, 49, 52) or on functional measures (30, 31, 50, 52), whereas some of the previous nutrition intervention studies did not report any major beneficial effects (53).

A recent meta-analysis of previous randomised controlled trials (114) concluded that oral multinutrient supplements after a hip fracture tended to reduce the number of complications. Nutritional therapy has been shown to reduce the hospital stay (31, 50, 52) and the number of complications (31, 50). In the current study, there was a tendency towards shorter hospital stays in the *CT* and *N* groups, but the main denominator for extended hospital stay appeared to be fracture healing complications.

Our data indicated that liquid supplementation alone has no effect on lean body mass. This finding is supported by a previous report (115), thus indicating that accretion of muscle requires an anabolic stimulus to complement the nutritional intake. Exercise may be the preferable anabolic choice (116), albeit it is difficult for many elderly patients to comply with this. In such circumstances, nandrolone therapy may be an option. In two previous reports (50) (52), it has been suggested that an oral protein-rich nutritional intake may have muscle anabolic effects in itself, and the authors suggest that the registered effects were caused by increased IGF-1 levels due to the protein intake. Low serum-IGF-1 levels in half of our patients and a low IGF-1/IGFBP1 ratio in 9 out of 10 patients indicate that this selected group of hip fracture patients was in an active catabolic state following their fracture. Inflammatory activity, as indicated by elevated CRP levels, triggered by the trauma and the surgical procedure, most probably explain the high catabolic activity. During follow-up, serum-IGF-1 levels increased in all three groups. In contrast to the study by Schürch *et al.* (52), we did not record a significantly higher increase of serum-IGF-1 in patients receiving protein-rich supplementation than in controls. This may be explained by our study being underpowered to answer this specific question, as a numerical increase in IGF-1 was more pronounced in the supplemented patients.

Another finding of the study was that a fracture healing complication had a significant negative impact on the nutritional outcome, such as weight and lean body mass. In the present study, fracture healing complications were, as expected, strongly correlated with a displaced fracture and a negative effect on the quality of life and resulted in a longer hospital stay mainly due to an increased number of reoperations. In the regression analysis, fracture displacement was, as expected, a main denominator for outcome regarding the quality of life. One study has compared IF and total hip replacement (THR) in displaced femoral neck fractures regarding nutritional data (117). A better functional and a more favourable nutritional outcome was reported in patients with a primary THR. The number of fracture healing complications at one year in the current patients with displaced fractures was unexpectedly high, i.e. 50%, probably reflecting the fact that the selected group of patients was older (mean 83 years) and had a lower BMI and more pronounced osteoporosis than patients in previous studies on femoral neck fractures. For comparison, in the previous studies (mean age 80 years) including relatively healthy elderly patients (*Studies II and IV*), the one-year fracture healing complication rate after internal fixation was 25% and 23%, and the two-year rate was 36%. This may support the trend towards a primary hip arthroplasty also in patients with a displaced femoral neck fracture and signs of malnutrition.

A likely explanation of the surprising finding that advanced age (>84 years) and a low BMI (<20.5 kg/m<sup>2</sup>) predicted a better outcome regarding the quality of life may be that these groups had low EQ-5D<sub>index</sub> scores before the fracture. Consequently, they were not susceptible to a major decrease in the quality of life. Still, their absolute values were lower also at follow-ups, compared to patients of a younger age and with a higher BMI.

We included only patients with a BMI <24 kg/m<sup>2</sup>. The criteria for malnutrition are controversial, but BMI is one of the more frequently used ones. In a recent review (118), it was suggested that the optimal range of BMI for elderly patients is 24 - 29 kg/m<sup>2</sup>. One reason for including only lean patients was previous data suggesting that nutritional intervention is more effective in very thin patients (30).

## Conclusion

Elderly female patients with femoral neck fractures often displayed protein-energy malnutrition. IGF-1 and its ratio with IGFBP-1 appeared to be good markers for the catabolic state of these patients. Thus, the determination of IGF-1 and IGFBP-1 may facilitate decisions on the treatment procedures in elderly hip fracture patients. Moreover, these patients often displayed cognitive dysfunction and reduced scores in the quality-of-life assessment, especially a lack of energy. The patients who were underweight had the worst scores in the quality-of-life assessment.

The intervention study supports the use of combined treatment with a protein-rich formula and nandrolone in lean elderly women with femoral neck fractures, as such treatment appears to have a positive effect on body composition as well as the functional outcome and quality of life. Fracture-healing complications also seem to negatively influence the nutritional outcome, and future nutritional studies should thoroughly analyse the influence of fracture type and fracture healing complications on outcome. Fracture-healing complications after a displaced femoral neck fracture treated with IF seem to be even more frequent in lean/malnourished women than indicated in

previous reports on unselected patients, which may support the use of a primary arthroplasty also in this selected patient group.

## LIMITATIONS

There are some obvious limitations in the studies in this thesis which need to be discussed. All assessments of the quality of life before the fracture were based on recall, which introduces the risk of recall bias. This is thoroughly discussed in the section Methods, Recall bias.

The number of patients in *Study VI* limits the statistical power, especially considering the effects of nutritional supplementation alone.

Few patients were lost to follow-up in the different studies, about 5% (*Study I* 6%, *Study II* 4%, *Study III* 4%, *Study IV* 3% and *Study VI* 8%). Their outcomes were reported, if possible, and the fact that they did not attend follow-up should not affect the interpretation and did not greatly affect the results.

The limited number of surgeons involved in *Studies III and IV* is both a weakness and a strength: a strength in the sense that both procedures were performed by experienced surgeons and thereby allow a fair comparison of the methods when correctly undertaken, but a weakness in terms of generalisability. We believe our results in the IF group are representative of what can be expected from IF when optimally performed. The low dislocation rate in the THR group may be due to the surgeon's experience but also to patient selection, surgical approach and optimised offset. Our conclusion also includes a recommendation that a primary THR in patients with femoral neck fractures should be performed by a surgeon who is well experienced in hip arthroplasty. Clearly, it is an error of judgement to let young and inexperienced surgeons perform these relatively difficult operations, as it is also an error to treat all displaced femoral neck fractures with internal fixation because it is a simple and fast procedure. Considering the consequences for the individual and the economic implications for society, a more differentiated approach is necessary.

## CONCLUSIONS

The EQ-5D appears to be a reliable and valid quality-of-life instrument in elderly patients with femoral neck fractures. There was a good correlation between the EQ-5D index scores, including subdimensions and other outcome measures such as pain, mobility, independence in activities of daily living status (ADL) and independent living status. The questionnaire response rate was high. *(Study I)*

The quality of life (EQ-5D index score) after internal fixation (IF) of a femoral neck fracture decreased from 0.78 before the fracture to 0.59 at 4 months and 0.51 at 17 months after surgery. The decrease was significantly larger among patients with fracture healing complications. *(Study I)*

The fracture healing complication rate at two years in patients with displaced femoral neck fractures treated with IF was 36% compared with 7% in patients with undisplaced fractures. The quality of life (EQ-5D index score) of patients with uneventfully healed fractures at two year was significantly lower in patients with primary displaced fractures, 0.51, compared to undisplaced fractures, 0.76. *(Study II)*

The responsiveness was high for both the EQ-5D and the SF-36, indicating that both instruments are suitable for use as outcome measures in clinical trials in elderly hip fracture patients. *(Study III)*

The results supports the notion that a primary total hip replacement (THR) should be the preferred primary treatment for an elderly, relatively healthy, lucid patient with a displaced femoral neck fracture. The complication rate was lower than after IF and the outcome regarding hip function and quality of life was generally better. *(Study IV)*

Nearly half of the elderly women with femoral neck fractures displayed signs of protein-energy malnutrition. Underweight was associated with reduced serum levels of IGF-1, muscle fatigue, cognitive dysfunction and a low quality of life rating (NHP), i.e. a cluster of factors which may unfavourably influence the postoperative course in a large proportion of patients with femoral neck fractures. *(Study V)*

Protein-rich liquid supplementation in combination with nandrolone given during 6 months to lean, elderly women after a femoral neck fracture may positively affect lean body mass, ADL and quality of life (EQ-5D). *(Study VI)*

Fracture healing complications had a negative impact on body weight, lean body mass and quality of life (EQ-5D). *(Study VI)*

## IMPLICATIONS FOR FUTURE RESEARCH

I believe that patients with femoral neck fracture deserve a more patient-related, rather than a strictly diagnosis-related, approach. Most patients with a femoral neck fracture are elderly and frail, but within this population there are several subpopulations, ranging from the independent living, lucid, healthy and active elderly patients to the institutionalised, cognitively impaired and bedridden patient.

For the patient with an undisplaced fracture, the preferred treatment is, without a doubt, internal fixation (IF). But, for patients with displaced fractures, we have different treatment options: IF, unipolar arthroplasty (cemented/uncemented), bipolar arthroplasty and the total hip replacement (THR), each with its different risk profile and potential.

There is growing evidence that the independent, lucid, relatively healthy patient benefits from a THR. Regarding other patient subgroups and other surgical procedures, i.e. hemiarthroplasty, we have to continue performing randomised controlled trial in order to find the optimal treatment and indications.

The following needs to be assessed regarding the treatment of displaced femoral neck fractures:

- The lower age limit for a primary THR
- The outcome after a bipolar arthroplasty
- The outcome after a unipolar arthroplasty
- The optimal treatment for the cognitively impaired patients
- The influence of nutritional support in lean/malnourished elderly patients in a high-powered study
- Cost-benefit analyses of different interventions
- The optimal rehabilitation after a femoral neck fracture

In my opinion, these future studies should, in addition to conventional outcome measures, also include the patient's perspective of the outcome, i.e. a measure of the quality of life.

Besides future research to optimise the treatment in this patient group, it is crucial that resources should be given to health-care service, i.e. departments of orthopaedic surgery, to allow an optimal primary surgical procedure and a decent follow-up regimen with the possibility for adequate and urgent treatment of possible hip complications. I am certain that such a treatment protocol will prove to be worthwhile not only for the patients but also for health-care givers and society as well.

## ABSTRACT IN SWEDISH

Det ökande antalet höftfrakturer är en utmaning för sjukvård och samhälle. Av gruppen höftfrakturer är de felställda lårbenshalsfrakturerna (cervikala femurfrakturer) de mest svårbehandlade och behandlingen hos äldre patienter är fortfarande kontroversiell.

Skruvfixation har varit den dominerande behandlingsmetoden i Skandinavien, medan primär höftplastik (ledersättning), halvplastik eller total plastik, varit vanligare i övriga Europa och Nordamerika. Det är av både humanitära och ekonomiska skäl nödvändigt att optimera den primära behandlingen för att uppnå bättre resultat och minska behovet av sekundär kirurgi. Vid utvärdering av behandlingsmetoder är det viktigt att analysera patientens upplevelse av resultatet. Två livskvalitetsinstrument, EQ-5D och SF-36, utvärderades hos patienter med cervikal femurfraktur och den hälsorelaterade livskvaliteten två år efter olika behandlingar registrerades.

EQ-5D visade sig vara ett lämpligt instrument för livskvalitetsregistrering hos äldre patienter med cervikal femurfraktur. God korrelation förelåg mellan livskvalitetsskattningen och andra utvärderingsvariabler som smärta, gångförmåga och förmåga att utföra dagliga aktiviteter (ADL). Både EQ-5D och SF-36 registrerade väl kliniskt viktiga förändringar i patienternas tillstånd.

Den av patienterna uppskattade livskvaliteten (EQ-5D) veckan före skadan visade god samstämmighet med värden från en åldersmatchad svensk referenspopulation. Livskvaliteten sjönk efter behandling med skruvfixation, speciellt hos patienter med frakturläkningskomplikationer. Frekvensen av frakturläkningskomplikationer efter två år var som väntat högre hos patienter med felställd fraktur jämfört med icke felställd fraktur, 36% respektive 7%. Patienter med komplikationsfritt läkta primärt felställda frakturer hade klart lägre livskvalitet jämfört med patienter med primärt icke felställda frakturer.

Skruvfixation jämfördes med total höftledsplastik vid behandling av äldre relativt vitala patienter med felställd cervikal femurfraktur. Efter två år var det fler höftkomplikationer efter skruvfixation än efter total höftledsplastik, 36% respektive 4%, och fler patienter var reopererade, 42% respektive 4%. Höftfunktionen och livskvaliteten (EQ-5D) var generellt bättre hos patienter som opererats med total höftledsplastik.

Nästan hälften av gruppen äldre kvinnor med cervikal femurfraktur visade tecken på undernäring (malnutrition). Låg vikt var associerat med muskelsvaghet, kognitiv dysfunktion och låg livskvalitet (Nottingham Health Profile). Proteinrikt nutritionstillskott i kombination med anabola steroider hade en positiv effekt på muskelmassa, ADL-funktion samt livskvalitet (EQ-5D) hos malnutrierade kvinnor med cervikal femurfraktur.

### Slutsatser

- EQ-5D är ett lämpligt instrument för utvärdering av den hälsorelaterade livskvaliteten hos äldre patienter med cervikal femurfraktur.
- Skruvfixation av felställd cervikal femurfraktur hos äldre patienter ger hög frekvens frakturläkningskomplikationer, och även patienter med läkt fraktur får en försämrad livskvalitet.
- Total höftledsplastik rekommenderas som primär behandling vid felställd cervikal femurfraktur hos äldre relativt vitala patienter.
- Behandling med nutritionstillskott i kombination med anabola steroider bör övervägas hos kvinnor med cervikal femurfraktur och tecken på malnutrition.

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