PhD Thesis

Influence of bone density and surgical treatment choice on failure of femoral neck fracture

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Preface and acknowledgements

My journey towards this thesis started in Svendborg Sygehus (SS) where I had my internship. The senior doctors were asked if they could think of a young doctor who could do some research for Odense University Hospital (OUH). Over the years I had developed an interest in entering into research, so when they asked me, I accepted, happy and proud. I had a meeting with Ole Ovesen who later became my main supervisor. We had a good working relationship, so when I began to think of the possibility of pursuing a PhD degree, Ole arranged for me to meet with senior hospital physician Jens Lauritsen and Professor, DMSc Søren Overgaard from OUH, and so I got employed at OUH.

The writing of the PhD protocol made very slow progress due to children and illness, and my supervisors began to doubt whether it would ever be finished. I thought I was stuck, but then Jens gave me the needed boost to finish the protocol. There was one problem, though: Money! I was not able to raise any money and therefore I turned to SS again. I owe my gratitude to SS, and especially Henrik Nohr, for giving me the opportunity to start this journey. I had the deepest respect for Henrik, his visions and his kindness. Even though I only knew him for one year, he had a great influence on me, and his death was a huge loss for SS. In SS I shared an office with a fellow PhD student, Allan, with whom I had some great laughs and discussions. It is always a pleasure to meet him.

When I came back to Odense again, my financial situation was still very unsure, and I owe my gratitude to my department for believing in me and under extraordinary circumstances securing me financially. The PhD study has been important for my academic education, and my most sincere gratitude goes to my three supervisors: Jens for keeping me on track and always having his door open for me; Søren for never setting the bar too low and for proving to me what a good professor should be like; Ole for taking care that I always had both feet on the ground and never lost the clinician's view.

Studying full time in Odense has been a great journey, and I am grateful to many people for supporting me: to the professor's secretary, Marianne Larsen, for always being kind and helpful; and to my fellow PhD students and co-workers in the research unit for the grand professional and social life. Special and heart-felt thanks go to the people at the office – I have had some very good laughs and discussions with them and have got new insights. There has always been a very good working atmosphere at the office.

It would not have been possible for me to engage myself completely in this work for the past three years, had it not been for my loving wife and my family.

I hope you will enjoy reading this thesis and sense the hard work behind it.

Content

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List of Abbreviations

BMD	Bone mineral density
CMR	Cortical marrow ratio
HA	Hemiarthroplasty
IF	Internal fixation
THA	Total hip arthroplasty

Summary

Femoral neck fractures are usually operated with either IF or HA, but a clarification is needed on the consequences of surgical choice, especially for the dislocated fracture. Compared to HA, IF is surgical faster and involves less initial surgical trauma, but treatment with IF has a high reoperation rate of approximately 35 %. HA has a reoperation rate of approximately 7 %, primarily due to deep wound infection and prosthesis complications such as loosening, dislocation and periprosthetic femoral fracture.

Failure is in this thesis defined as major reoperations. Predictors for increased risk of failure of IF can after a literature review be grouped into three categories:

Patient-related factors	age, gender, and neurological diseases
Surgeon-related factors	quality of reduction, implant positioning, surgeon experience and time to surgery
Implant-related factors	implant design

The most important predictors seem to be fracture displacement, implant positioning, quality of reduction, and age, and the first two predictors are confirmed in the papers of this thesis. Predictors of minor importance are gender, surgeon experience, time to surgery, and implant design. According to the literature another important factor for failure of IF is fracture healing which mainly consists of three elements: blood supply, bone contact, and stability.

This thesis also investigates BMD as a potential predictor for increased risk of failure. If low BMD is a predictor then a quick confirmation is needed before the surgical treatment is decided. The thesis therefore examines a self-developed geometrical measure – Cortical Marrow Index (CMR) – for low BMD on x-ray images. CMR can with a high positive predictive value find or exclude low BMD for 38 % of the cohort. BMD, however, proved to have little influence on the failure of IF in femoral neck fractures.

Predictors for increased failure of HA can after a literature review also be grouped into the same three groups as for IF:

Patient-related factors	age, gender, hip disorders
Surgeon-related factors	surgical approach, surgeon experience
Implant-related factors	Head (bipolar vs. unipolar), cement, coating, and stem design

In the literature there seems to be no difference in risk of failure when comparing unipolar HA with bipolar HA, the surgical approach, or the surgeons experience. However, there is an increased risk of failure associated with lower patient age, male gender, and with some uncemented stem designs. One of the papers in thesis finds a higher failure rate for older uncemented HA compared to cemented HA, especially

after 5-10 years. The uncemented HA do not seem to benefit from hydroxy-apatite coating when failure rates for the uncemented HA were compared to those of the cemented HA.

Generally, in studies assessing failure, the sample sizes are too small to detect small risk of increased failure, since the increased mortality in femoral neck fracture patients are not taken into account.

Danish summary

Collum femoris fraktur bliver oftest opereret med intern fiksation (IF) eller hemialloplastik (HA), men der mangler belysning af konsekvenserne ved operationsvalget, specielt for den dislocerede fraktur. IF er i forhold til HA et hurtigere og mindre kirurgisk indgreb, men IF har en høj reoperation på ca. 35 %. HA har en reoperationsrate på ca. 7 %, primært som følge af dyb sårinfektion og protese komplikationer såsom løsning, luksation og periprostetisk femurfraktur.

Behandlingssvigt er i denne afhandling defineret som større reoperationer. Prædiktorer for øget svigt af IF kan efter en litteratur gennemgang inddeles i tre kategorier:

Patient-relaterede faktorer	alder, køn og neurologiske sygdomme
Kirurg-relaterede faktorer	kvaliteten af reposition, implantat placering, kirurgiske erfaring og ventetid til operation
Implantat-relaterede faktorer	implantat design

De vigtigste prædiktorer synes at være fraktur dislokation, implantat placering, kvaliteten af reposition og alder, hvor de to førstnævnte bekræftes af afhandlingens artikler. Prædiktorer med ringe betydning for svigt er køn, kirurgisk erfaring, ventetid til kirurgi og implantat design. En anden vigtig faktor for svigt af IF, ifølge litteraturen, er frakturheling, som hovedsagelig består af tre elementer: blodtilførsel, knogle kontakt og stabilitet.

Denne afhandling undersøger også knoglemineral tætheden (BMD) som en potentiel prædiktor for øget svigt ved IF. Såfremt lav BMD er en prædiktor, kræver det en hurtig bekræftelse før en given operation. Derfor undersøger afhandlingen et selvudviklet geometrisk mål – Cortical Marrow Index (CMR) - for lav BMD på røntgenbilleder. CMR kan med en høj positiv prædiktiv værdi finde eller udelukke lav BMD for 38 % af kohorten. BMD har dog i afhandlingen vist sig at have ringe indflydelse på svigt af IF ved collum femoris fraktur.

Prædiktorer for øget svigt af HA kan efter litteratur gennemgang også inddeles i de samme tre grupper som for IF:

Patient-relaterede faktorer	alder, køn, hoftelidelser
Kirurg-relaterede faktorer	adgang, kirurgisk erfaring
Implantat-relaterede faktorer	caput (bipolar vs unipolar), cement, overfladebehandling og stem design

I litteraturen synes der ikke at være nogen forskel i risiko for svigt, når man sammenligner unipolar HA med bipolar HA, den kirurgiske adgang. Der er imidlertid en øget risiko for svigt forbundet med lavere patient

alder, det mandlige køn og med nogle ucementerede stem designs. Den ene artikel i afhandlingen finder en højere svigtrate for ældre ucementeret HA i forhold til cementerede HA, især efter 5-10 år. Den ucementeret HA synes ikke at drage fordel af hydroxy-apatit overflade behandlingen, når svigtraterne sammenlignes med den cementerede HA.

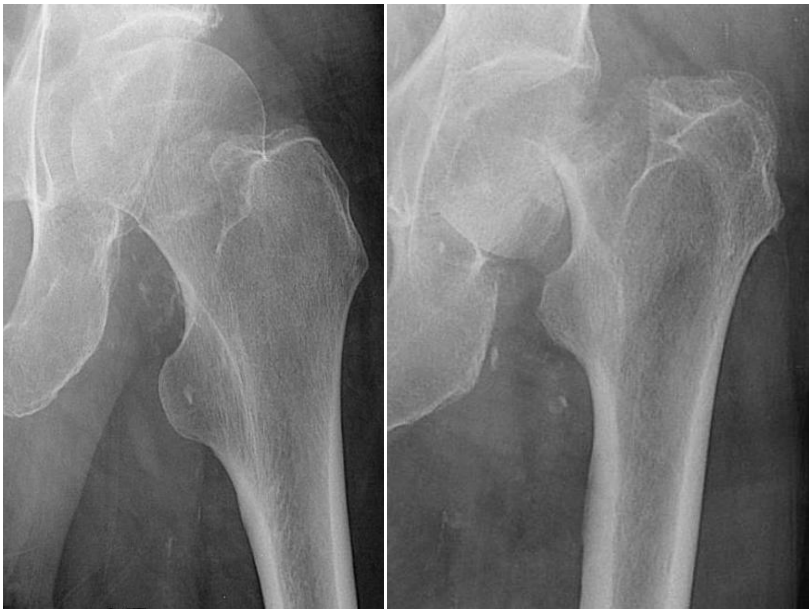
Overordnet kan det dog konkluderes ved litteraturgennemgangen, at de studier som belyser behandlingssvigten ikke er store nok til at finde de små risici for øget svigt, da der ikke er taget højde for den øgede mortalitet hos collum femoris fraktur patienterne.

Background

Femoral neck fracture in general

Hip fracture is the general term for three specific fractures: the femoral neck fracture, the trochanteric fracture, and the subtrochanteric fracture [1]. The latter fracture is the least frequent totalling 5-8 % of all hip fractures; the trochanteric fracture accounts for 31-41 %, and the most frequent fracture, the femoral neck fracture, accounts for 51-56 % of all hip fractures [2-4]. A femoral neck fracture is intracapsular [1] and is usually classified as a displaced or an undisplaced fracture (Fig. 1), which is a modified version of the original four Garden stages [5, 6]. Fractures can also be classified using other systems such as the AO classification [7] and the Pauwel classification [8], among others.

Fig. 1 Left: an undisplaced fracture. Right: a displaced fracture



The hip fracture is a worldwide challenge particularly in the developed countries [9, 10]. Despite indications of decreasing incidence, there is an increase in the overall number of hip fracture patients in northern Europe [11-13]. Every year approximately 10,000 people in Denmark experience a hip fracture and the typical patient is an 80-year old female [14]. Of these patients, 9 % also experience a second fracture within the first year after the first hip fracture [15, 16]. The physical function range from not being able to walk (3 %) to walking without aid (50 %) [4], and approximately 42 % have cognitive impairment [17]. These patients are fragile with a co-morbidity percentage of 55 % (ASA score above 2) [2]. Thirty days after the hip fracture, the mortality rate is 12 %, and after one year 26-37 % [3, 18], which is a threefold increase in the one year mortality [19] or an excess mortality of 8.4-36 % [20]. These numbers reflect the great heterogeneity of the hip fracture patients.

Treatment

Historically, femoral neck fractures were treated conservatively with traction, plaster, and bedrest [21]. In 1921, Marius Nygaard Smith-Pedersen developed a flanged nail which marked the beginning of the surgical treatment era [22], and in 1943, Moore and Bohlman reported the use of an HA [23]. In terms of complications, the surgical treatment is not very different from the conservative treatment [24], but it gives better anatomical results, shorter hospital stay, and less loss of independence six months after injury [25]. Although IF and HA have been the standard treatment methods for well over 50 years, there are great worldwide differences [26]. It has been generally agreed to use IF on femoral neck fracture patients younger than 70 years as well as on patients above 70 years with an undisplaced fracture. The diversity lies in the treatment of the displaced fracture in patients above 70 years where the treatment options are usually IF, HA, or THA [27, 28]. Girdlestone and nonoperative treatment can be used for special cases, e.g. bedridden, senile patients.

IF has a clear advantage due to the less initial surgical trauma with less blood loss and shorter operating time [29-32]. The major disadvantage is a high reoperation rate which varies from 10-57 % [33]. Primary arthroplasty has a much lower percentage of reoperations (4-32 %) [33], and patients experience less pain and better hip function after 1-2 years compared to treatment with IF, but at the expense of a higher risk of deep wound infection and prosthesis complications such as loosening, dislocation, periprosthetic femoral fracture, as well as risk of acetabular erosion [29-32]. Over the last decade there has been a substantial increase in the use of HA for displaced femoral fractures, and this treatment is today used in 67-83 % of the cases in the Scandinavian countries [2-4]. THA is also an option for the limited subgroup of elderly patients who are active, independently living, and cognitively intact [34]. Compared to HA, THA has lower revision rates and better functional outcomes but higher dislocation rates [35-38].

Failure

This thesis focuses on IF and HA, and failure is here defined as procedures leading to major reoperation:

- IF failure: avascular necrosis, non-union, osteosynthesis failure, infection, penetration of IF material through caput, new fractures around implant.
- HA failure: dislocation, infection, loosening, periprosthic femoral fracture, acetabular erosion, intraoperative fracture.
- Major reoperation: Change of IF (resection, arthroplasty, or new hip fracture), loss/change of HA or pereprosthetic fracture. Simple removal of IF and dislocation of HA is not included.

Because of the high failure rate for IF, there has been an interest in finding predictors for fixation failure [39]. These predictors can be grouped into the following three categories: *Patient-related factors* are e.g.

age and gender: there is an increased risk of non-union with older age [39, 40], and there does not seem to be any difference between the genders [39, 41]. *Surgeon-related factors* are e.g. quality of reduction and implant positioning: poor reduction results in higher non-union rates [42-44] and inferiorly placed IF leads to higher failure rate [42, 45]. *Implant-related factors* refer to the use of older IF designs that lead to an increased risk of failure [46]: screws are better than smooth pins, and telescoping systems are better than rigid ones. For newer IF designs there do not seem to be any *implant-related factors* contributing to fixation failure [47, 48]. Good bone contact between bone fragments is important in fracture healing, and for femoral neck fractures there are lower reoperation rates for undisplaced (11 %) compared to displaced fractures (40 %) [31, 49]. A proposed mechanism for failure is osteoporosis which is an important risk factor for hip fracture [50]. Osteoporosis seems to delay the healing of fractures in animal studies, but clinical evidence is still lacking [51, 52]. Several experimental studies have shown that osteoporosis affects the strength of osteosynthesis [53-55], but the influence of osteoporosis on clinical fracture fixation is unclear [56]. Several medications and diseases can alter bone formation and therefore possibly affect fixation failure but is not in the scope of this thesis.

For HA the search for failure predictors can be grouped into the same 3 categories as for IF but the focus has been on the *implant-related factors* such as uni-/bipolar heads, cemented/uncemented stem, and hydroxy-apatite coating. The debate on unipolar versus bipolar HA is ongoing [57], but there is to this date no definitive evidence of any difference in outcome between the two types [58-60]. The latest Cochrane review on the difference between cemented and uncemented HA concluded that cemented prostheses have reduced post-operative pain and lead to better mobility compared to uncemented prostheses [58], but this only applies to the older types of uncemented HA. One randomised controlled trial [61] has compared a cemented HA with an uncemented hydroxy-apatite coated HA and demonstrated good results for both HAs with no difference in complications, mortality or functional outcome after one year.

A newly published study from the Norwegian Hip Fracture Register [62] showed a significantly higher five-year survival of cemented HA compared to the uncemented HA (almost exclusively hydroxy-apatite coated HA). The vast majority of performed RCTs have a maximum follow-up time of two years, so only little knowledge exists on the long-term performance of both IF and HA. The long-term result is becoming more and more important for the quality of patient treatment, especially considering the increasing life expectancy (10.3 years for a 75 year old male and 12.2 for a 75 year old female) [63] and the changes in demographics with a growing number of elderly people [11-13]. Three RCTs with a follow-up period over 10 years [64-66] have compared IF and HA. The studies showed that IF had an increased reoperation rate, but there was no difference in functional outcome or residual pain between the two groups. These studies, however, did not include uncemented hydroxy-apatite coated HA.

Measurements of bone mineral density

In 1994 the World Health Organization suggested a definition of osteoporosis [67]. It was defined as 2.5 standard deviation below peak bone mass (t-score < -2.5) of young adults [68], and this definition has been used since. Since then other definitions for osteoporosis have been included such as low-energy fractures in the hip or spine [69]. The gold standard for measuring BMD (g/cm^2) is a dual-energy x-ray absorptiometry (DXA) scan which combines two different low-dosage x-rays to differentiate bone mineral and soft tissue, and BMD reflects an estimate of the true volumetric density [68]. Besides DXA, other techniques are available for measuring bone density such as quantitative ultrasonometry and quantitative computed tomography. In this thesis, the focus is on simple x-ray measures that would allow for an interpretation of BMD.

With the future burden of osteoporosis in mind [70] it is of interest to find different ways of diagnosing low BMD. The Singh Index [71] is the oldest and best known geometric measure, but it is not reliable [72-76] and does not seem to correlate well with BMD [72, 73, 75, 77-81]. Several other geometrical measures have been defined [75, 78, 82-86], but only canal bone ratio [84] has shown good reliability and correlation with BMD. However, the study is on cadavers, and canal bone ratio uses a fixed measurement point which does not account for the morphological differences of small and large femora. Radiogrammetry is used to measure bone density in metacarpal bones and have good correlation with distal forearm BMD [87]. Radiogrammetry measures cortical thickness and therefore using cortical thickness in the hip area for bone density measurement is interesting.

Aim

The overall aim of this study was to investigate femoral neck fractures in patients treated with IF or HA in relation to short and long term failures. Osteoporosis was taken into consideration as a potential predictor for short term failure, and cortical marrow ratio (CMR) was used to assess low BMD on x-rays.

Paper 1: Aim: to evaluate CMR in terms of reliability and diagnostic accuracy for BMD levels

Hypothesis: Using DXA scans in a clinical setup is not feasible compared to analysing the existing x-rays using geometry. CMR is considered an aid in diagnosing low BMD.

Paper 2: Aim: to evaluate the effects of low BMD on failure of internal fixed femoral neck fractures.

Hypothesis: using IF in the femoral head often leads to lack of good fixation. This could be due to osteoporosis which is considered a potential predictor of failure.

Paper 3: Aim: to compare reoperation rates for 75+ year-old patients with displaced femoral neck fractures treated with IF, cemented HA, and uncemented HA (with and without hydroxy-apatite coating) with 12 to 19 years follow-up.

Hypothesis: IF is inferior to HA within the first 2 years, but there is little knowledge of the long term perspectives. For long term hip survival there is no indication of a difference between failure of IF and HA.

The three papers should be read as an integral part of this thesis.

Methodological consideration

When the three papers were designed, a number of different biases were discussed. In the paragraphs below, the different biases are discussed based on papers [88-91].

Selection bias

Sample bias occurs if the sample does not adequately reflect the spectrum of characteristics in the target population. The patient material studied in papers 1 and 2 is the same as in a previous consecutive study [92] that did not include patients who died before the DXA-scan (average three months). This gave a one-year survival rate of 6.4 % which might result in problems with external validity. In practice, however, this would be a minor problem because only a small number of the patients would experience a failure before death, thereby not introducing a major bias. In paper 3 a sample bias is introduced due to the difference in comorbidity in the four groups: patients in better health are likely to be more active, thereby increasing the risk for reoperations (periprosthetic fracture and wear). The comorbidity was especially low in cohort 4, but this cohort was very unique because the patients had been treated at a hospital that used a modern uncemented hydroxy-apatite coated HA which was very seldom at the time. This hospital also used comparable guidelines, and by adjusting for comorbidity in the survival analysis the bias would become very small.

Procedure/channeling bias occurs when patients may or may not be offered a treatment because of coexisting morbidities or poor prognosis. This is probably the case for cohorts 2-4 in paper 3 in which some of the displaced fractures were treated with IF instead of HA, probably due to the health status of the patients. Surgeons at each hospital independently informed the author that a patient who was active and seemed in good health (lower physiological than biological age) would sometimes be treated with an IF instead of an HA. The importance of this bias seems small because the numbers are small and similar in the three cohorts.

Information-observation bias

Verification/work-up bias refers to potential differences in the manner in which disease status is determined. This is a problem when carrying out studies that use two different code sets as was the case in paper 3. Since 1994, diagnosis classification has been done according to the Danish version of the International Classification of Diseases (ICD), tenth edition [93], but prior to that time the ICD-8 was used [94]. The procedure codes were not changed from ICD-8 to ICD-10 in 1994, but one year later, in 1995. This resulted in three time periods with different codes, potentially leading to different biases. To accommodate for this, an extended search for all possible codes was used and thoroughly examined by hand and cross checks in STATA. The coding problem also existed in the National Registry of Patients (NRP) for dislocation of HA because some hospitals did not admit the patients and reduced the dislocation in the Emergency Room. Data on outpatients and emergency visits were not included in the NRP until 1995 [94].

Response bias occurs e.g. when missing data are present non-randomly for study subjects. There may be a bias for IF as some bedridden patients in nurseries have a functional girdlestone after IF, but these patients will not get a reoperation. This reflects a reluctance to perform reoperation after IF in certain patients and the reluctance is likely to be higher for IF than for HA because most reoperations with HA is associated with pain for the patient. In paper 3 bias is introduced due to conservatively treated periprosthetic fractures, but since it was not possible to access all patient files, the endpoint of reoperation was chosen.

Diagnostic-review bias occurs when reference test results are not definitive. The initial analysis for bone density showed that 53 % of the cohort studied in paper 2 had low total hip BMD and 84 % had low femoral neck BMD. These numbers seemed a bit high, and the reference material for diagnosing osteoporosis was obtained. In 2005-6, when the initial prospective study was conducted, the Hologic reference material was used but this was later changed to NHANES III [95]. This resulted in 35 % of patients with low total hip BMD and 53 % with low femoral neck BMD. Similar discrepancies can be found when comparing Hologic and Lunar normative data [96]. We found it important to use population-based reference values as otherwise there would be potential false positive or negative findings [97]. The reference data from the Dept of Endocrinology, Odense University Hospital, were slightly different from NHANES III suggesting that the data were altered for a Danish reference:

Total hip	Female:	BMDpeak=0.942	SD=0.122
	Male:	BMDpeak=1.033	SD=0.151
Femoral neck	Female:	BMDpeak=0.849	SD=0.111
	Male:	BMDpeak=0.930	SD=0.136

As hip BMD measurement we chose to use total hip BMD as several studies investigating the reproducibility of total hip and femoral neck measurements have shown total hip BMD to be more reliable [98-100]. Total hip BMD is also recommended by The Danish Bone Society in their clarification report [69].

Imperfect-standard bias occurs if the reference standard is not 100 % accurate. The DXA-scan measures bone mass which is the primary predictor for bone strength, and 80 % can be directly related to BMD [101, 102]. Although there is a good correlation between BMD and bone strength [103-108], adding a geometrical measure to BMD was found to be highly predictive of bone strength [104] and could account for 90 % of the maximal bone strength [108]. Even though BMD measurement is an imperfect surrogate measure for bone strength, it is the best and was therefore chosen [69].

Measurement bias relates to discrepancies in measurements obtained. Fracture displacement was assessed using the Garden criteria [5], but the reliability of the classification is low when using the four-grade scale and acceptable when using the simplified non-displaced vs. displaced version [109]. Palm et al [110] found significantly more failures of undisplaced fractures if there was more than 20 degree posterior tilt on the axial x-ray. The problem was discussed intensively and in order to compare our results to the literature, the simple Garden classification was used. For quality of reduction there are several classification systems but they all seem to be of equal reliability [111]. We chose the Garden alignment index due to familiarity because the thesis by Frandsen [112] originates from our department. We did, however, modify it to keep it as simple as possible. Instead of having two cut off points for the angle measurements on the axial x-ray, 20 degree was chosen inspired by the work of Palm et al [110]. This should in theory make the measurement more reliable as seen when downgrading the Garden classification [109]. For implant positioning, there seemed to be no studies assessing the reliability of implant grading, but the grading by Schep et al [42] with a 6 point score had shown good results and seemed very simple. It had to be modified because the Uppsala screws used in our department should be placed centrally on the axial view and not posteriorly as in the Schep et al study [42].
When reviewing the literature for the geometrical measures, we found only one study with good reliability and BMD correlation [84]. However, their method was difficult to apply in a clinical setting. The grading was therefore modified during a pilot study where the main focus was on making the CMR measurement reproducible, reflecting the physiology of the femur.

Transfer bias refers to subjects being lost to follow-up. It is not possible to have complete follow-up in any study. In order to minimize the bias, complete hospital history from each patient was obtained through NRP. Every contact to any hospital is recorded and even the coding is quite good [113]. It was important to verify the reoperations at a case level. Therefore all possible reoperations were searched in patient files and validated. In retrospective cohorts, compared to prospective cohorts, there is always an uncertainty in the completeness of patient enrolment, especially because the coding is not necessarily good enough [114]. In order to get as close as possible to a prospective enrolment, we searched the region-based administrative databases using procedure and diagnosis codes. This resulted in three lists that were cross-checked and the information found on the patients was validated using patient files.

Performance bias refers to different outcomes between surgeons. It was important that the guidelines in paper 3 were the same for all cohorts considering the several different surgeons. If the number of surgeons was 2-3 in each hospital, the risk for performance bias would be higher. Also there is a possible performance bias for HA compared to IF according to Bhandari et al [48] who showed that the surgeons doing HA operations are more experienced than those doing IF operations.

Confounding

Confounding occurs when the effect of the exposure is mixed together with the effect of another variable, leading to a bias [115]. Confounding variables are not a problem when recognized and measured because a statistical model can adjust for them. Especially for paper 2 it was important to find possible confounding variables in order to determine the real influence of bone density on failure. The literature was searched and the study was designed to incorporate all variables and adjust for them in a survival analysis. There was, of course, still a possibility for unmeasured confounders which could influence the result.

Summary of results

Paper 1: **Cortical Marrow Ratio: A revised method to detect low bone mineral density in plain x-rays of the hip**

CMR was very reliable with an interrater intraclass correlation coefficient (ICC) of 0.87-0.98 and an intrarater ICC of 0.86. The diagnostic accuracy had a positive predictive value of 81 % (CI 54;96) for finding low BMD and of 94 % (CI 80;99) for excluding low BMD. In combination CMR, used as a screening test, can assess whether patients have low BMD or not for 37.9 % of the cohort. Based on postoperative x-rays, low BMD or not could be settled for 46.0 % of the cohort.

Paper 2: **Bone density in relation to failure in patients with osteosynthesized femoral neck fractures**

The failure rate was 22 % (95 % CI 12;39) for the undisplaced fracture and 66 % (95 % CI 56;76) for the displaced fracture after two years. The survival analysis showed no association of low hip BMD and failure (hazard ratio 0.82, 95 % confidence interval (CI) 0.46;1.47, p=0.506). The only covariate to show significance was implant positioning. A subgroup analysis of the undisplaced fractures revealed no statistical significance of low BMD and failure (hazard ratio 6.22, 95 % CI 0.53;73.4, p=0.147) but there is a trend when comparing to the main analysis.

Paper 3: **Reduced reoperation rate of cemented versus uncemented hemiarthroplasty and internal fixation of displaced femoral neck fracture with 19 years follow-up of 75+ year old patients**

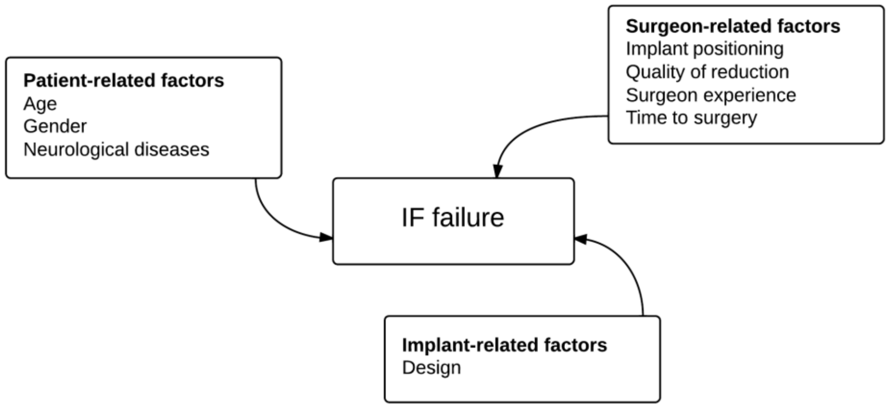
At the end of follow-up cemented HA had a reoperation rate of 5.3 %, the rate for IF was 18.3 %, for uncemented HA 10.8 %, and for uncemented hydroxy-apatite coated HA 15.9 %. Within two years the reoperations done for IF was 87.9 %, for uncemented HA it was 81.8 %, for cemented HA it was 63.6 %, and for uncemented hydroxy-apatite coated HA it was 56 %. The main reason for failure was for IF osteosynthesis failure (85 %) and for HA periprosthetic fractures (59 %, 55 %, 56 %). The survival analysis with cemented HA as reference (hazard ratio = 1) and adjusted for co-morbidity, age, and gender revealed higher hazard ratios of failure for IF (3.76, CI 1.89 – 7.48, p=0.000), uncemented HA (2.19, CI 1.06 - 4.51, p=0.035), and uncemented hydroxy-apatite coated HA (3.61, CI 1.77 – 7.35, p=0.000).

Overall discussion

The main topic of this thesis is failure, and the discussion will elaborate on this with a focus on failure of IF and HA treatment in elderly patients with displaced femoral neck fractures.

Failure and IF

Fig. 2 Elements with influence on IF failure



There are several elements that influence failure after IF. The discussion below is based on Figure 2.

Patient-related factors

There is a clear trend in the literature for an association between risk of failure and increasing age [39, 41, 42, 116-119]. Two large studies of over 1000 patients [39, 41] show a clear correlation between increasing age and increased risk of failure. Both studies tabulate the results by displacement, gender and age but fail to account for other potential predictors in the same analysis. Barnes et al [41] did not have the appropriate statistics available in the 1960's, and Parker et al [39] did not include other potential predictors such as implant positioning and quality of reduction in their study. Parker et al [39] made an important observation: There was initially no association between increasing age and risk of failure, but adjusting the analysis for patients dying within one year made the association clear. The appropriate statistics to use when analyzing failure predictors is therefore the survival analysis, which censors deaths [120]. Assuming that the results for undisplaced and displaced fractures are done separately, Parker et al [39] also made a power calculation pointing out that a minimum of 270 patients are required to detect a significance at the 90 % level. Three studies [44, 121, 122] did not take the above-mentioned factors into account which is probably the reason why they did not show an association between increasing age and risk of failure. Paper 2 uses survival analysis and adjusts for potential predictors, but it has a power problem and is not designed to investigate age in relation to increased risk of failure.

With regard to gender three studies [39, 44, 123] find an association between risk of failure and gender whereas five studies do not [41, 116, 117, 121, 122]. Bearing the Parker et al [39] power calculation in mind, there are only four studies of interest. Two of these [39, 123] favor an association and two do not [41, 116], although there is largely the same number of patients in each study group. There does not seem to be any difference in the quality of the studies, and thus no clear evidence for an association between gender and risk of failure according to these studies. As for the age and failure, paper 2 has power problems and is not designed to investigate gender in relation to failure.

Other *patient-related factors* that could be considered are neurological diseases. In 2006, a review on Parkinson's Disease [124] concluded that there was no clear evidence for either IF or HA even when looking at the dislocation rates. Based on the very few studies on hemiplegic, there is an indication that patients have high failure rates when treated with IF [125], and that they may benefit from treatment with HA or THA [126]. The last neurological disorder to be mentioned here with regard to failure rate is dementia: Two RCTs include only patients with dementia and both studies show reduced reoperation rates for HA compared to IF [127, 128].

Surgeon-related factors

Implant positioning has been investigated in many studies. Eight studies find an association between implant positioning [41, 42, 117, 121, 129-132] and risk of failure, whereas five studies do not [43, 45, 122, 133, 134]. Many of the studies investigate potential parameters separately, and the largest study by Barnes et al [41] (n=1503) shows an advantage of inserting a nail in the center of the femoral head and 0.5-1 cm from the articular cortex. Studies analyzing parameters separately would have to be quite large in order to reach significance. Frandsen et al [129] made a scoring system for the nail position using anterior-posterior and axial views: "good" if inserted in the centre, "fair" if inserted posteriorly and/or inferiorly, and "poor" if inserted anteriorly and/or superiorly. If the tip of the nail was not within 1 cm of the articular surfaces of the femoral head, the position of the fixation appliance was degraded one group. This was the first attempt to incorporate several implant positions in one scoring system. Schep et al [42] took it one step further by incorporating the three point fixation principles [135] for IF. The scoring system incorporated position of the screws in the femoral head, distance to articular surface of the femoral head, angulation of the screws, and position directly over calcar. A maximum of 6 points could be achieved and 5 points were considered adequate fixation. The study showed that poor implant positioning had significant effect on the outcome. Of studies not showing an association between implant positioning and risk of failure two used a scoring system [43, 133]. The study by Heetveld et al [43] had a p-value of 0.07 for the association between implant positioning and clinical failure, but it might have been different if they did not have a poor agreement between the raters (kappa = 0.16 ± 0.1). Hoelsbrekken et al [133] applied a different scoring system. They used three of the six points developed by Schep et al [42], and created two new ones, but a moderate agreement was barely reached (kappa 0.42). This scoring system might therefore not be as sensitive as the one used in the Schep et al study. Paper 2 uses the scoring system by Schep et al [42] and finds a clear significance between implant positioning and risk of failure.

Another *surgeon-related factor* is quality of reduction, and almost all studies find an association between risk of failure and quality of reduction. Eight studies [43, 44, 117-119, 122, 132, 136] investigated individual parameters, and especially reduction to a varus position was found to be significant. Seven studies [41, 42, 121, 129, 133, 137, 138] used the Garden alignment index [129] to some extent and all studies find an association between quality of reduction and risk of failure. The Garden angle [5] is in the anterior-posterior x-ray an approximately 160 degree angle from the medial trabeculae in the femoral head with the medial femoral cortex, and in axial view the angle is 180 degrees. Frandsen [129] used this information to make an alignment index in three stages: Good reduction – frontal angle 160-175 degrees and a lateral angle less than 15 degrees; Fair reduction – frontal angle either 150-159 degrees or 180-189 degrees and/or lateral angle 15-25 degrees; Poor reduction – frontal angle either less than 150 degrees or more than 190 degrees and/or lateral angle more than 25 degrees. Paper 2 uses a slightly modified version of the Garden alignment index and shows no association between quality of reduction and risk of failure. If the association between quality of reduction and risk of failure is smaller than the association for implant positioning then paper 2 should have been larger in order to find the association. Two studies [130, 134] did not find an association between quality of reduction and risk of failure and their main problem is a small number of poorly reduced fractures.

The difference between an experienced and less experienced surgeon has proposed as a *surgeon-related factor* for increased risk of failure. Strömqvist et al. [139] included 626 femoral neck fractures and for the undisplaced fractures (n=150) there was no statistical difference for the complication rate between the experienced (7 %) and less experienced (9 %) surgeons. However, for the displaced fracture (n=476) the less experienced surgeons had a 37 % complication rate compared to 27 % for the experienced surgeons. Holmberg et al. [140] included 2418 femoral neck fractures and 93 % were IF. Early redisplacement was higher if the surgeon was less experienced but the result has a confounder in the Thornton nail which was used more in the less experienced group. The total complication rate between surgical departments (primarily less experienced surgeons) and orthopaedic departments was not different. Palm et al. [141] showed that unsupervised junior surgeons had higher reoperation rate (29 %) compared to the experienced surgeons (15 %) but this accounts for all types of hip fracture surgery. There is a learning curve in IF for femoral neck fractures [142] but it seems not clear if low experience leads to more reoperations. In paper 3 the hospital that treated their patients with IF had all operations supervised by a senior registrar. A high experience level could be a reason for the low reoperation rate of 18.3 % but the reoperation rate for patients with a displaced femoral neck fracture in Denmark 2011 was also 18 % [3].

Time to surgery has been proposed as factor for increased risk of failure and is of course not necessarily directly related to the surgeon, but is here placed in the *surgeon-related factor* group rather than in the *patient-related factor* group. Six studies [41, 118, 140, 143-145] finds no association of increased risk of failure and time to surgery within one week. The two largest studies [41, 140] (1066 and 2251 patients) finds, however, an increased risk of failure when the time to surgery is above one week. Three smaller studies [136, 146, 147] finds an increased risk of failure when the time to surgery is more than 24-48 hours but they all have power issues and adjustment for co-morbidity are not applied. Two studies by Manninger et al [148, 149] shows an association if the delay of surgery is more than 6 hours. There are though major concerns regarding the quality of the two studies: they are retrospective and adjustment for co-morbidity and age are not done. There is no solid evidence for an increased risk of failure associated with time to surgery, but further studies on surgery within 6 hours are of interest.

Implant-related factors

At least 100 different implants have been used for IF of femoral neck fractures [150], and two meta-analyses and two reviews have investigated different implants in order to determine which implant to recommend [33, 47, 48, 151]. The conclusions are that screws are preferable to smooth pins, although the addition of a hook pin eliminates this difference [151], and sliding hip screws may have marginally lower risk of fracture healing complications than the parallel screw technique but at the expense of an increased risk of wound healing complications [47, 48]. Heetveld et al [33] mention that factors such as fracture reduction, implant positioning and other aspects of surgical technique are probably of greater importance with regard to fracture healing complications than the actual choice of implant, and even the degree of osteoporosis may affect fracture healing.

Failure and bone density

Three factors are important in fracture healing (Fig. 1): blood supply, bone contact, and stability [52, 152]. Osteoporosis affects stability, which has been shown in several experimental studies [56, 153]. This could be due to a lower fracture healing rate and bone repair as seen in animal studies [51, 52]. The ovariectomized rat model has several disadvantages such as differences in bone metabolism compared to humans, and lack of prominent decrease of bone mass after ovariectomy [52]. There is only one study on the influence of osteoporosis and fracture healing time in humans that finds a significant delay in older osteoporotic patients [154]. The study includes 66 patients with femoral shaft fractures treated by intramedullary nailing, but the two study groups differ regarding age and gender, and the estimation of osteoporosis is based on x-rays instead of DXA-scan. The same problem is seen in the majority of clinical studies investigating bone density and failure – the bone density measurements are done on x-rays. Only one of these geometrical measures [84] has shown high reliability and correlation with BMD. The other geometrical measures for bone density have too poor a reliability or correlation with BMD to be used in a clinical setting (details can be found in paper 1 and the methodological consideration section of this thesis). There are only two studies using BMD directly as a measure of bone density [155, 156]. Heetveld et al [155] found no difference in BMD in patients with fixation failure compared to the group without failure but failed to adjust for confounders even though they had information on age, gender, implant positioning and quality of reduction. The only study that included all known potential confounders in their analysis [156] found that patients with a registered ICD-9-CM code for osteoporosis had a hazard ratio of 7.8 for revision surgery. There are severe measuring biases because the prevalence of osteoporosis is most likely underestimated (9 %) when compared to other studies [157, 158] (up to 88 %), and the osteoporosis diagnoses was also based on low spine BMD and therefore not affecting the IF of the femoral neck fracture.

Paper 2 evaluates the effect of low BMD on risk of failure and adjusts for the above-mentioned potential predictors of failure. It shows no association between low BMD and risk of failure and therefore the question is whether this is true or whether it is a statistical power issue. The sub-analysis of the undisplaced fracture indicates that it is a power problem because the hazard ratio is markedly different compared to the main analysis and a sample size calculation for paper 2 reveals n=1682 (power 0.8, failure 0.5, censoring 0.25 and HR 0.8). Undisplaced fractures have a reoperation rate between 4.1 and 18.7 % in studies including over 200 patients [159-161]. An article from the Norwegian Hip Fracture Register found 4,468 undisplaced femoral neck fractures treated with IF and a reoperation rate after one year of 9.4 % [49]. Comparing the undisplaced fracture with the fracture healing factors would not show any alterations in the blood supply and bone contact which indicates that the main problem lies within the stability of the IF. One of the main predictors of failure for the undisplaced fracture could therefore be low bone density.

Bone density on x-rays

If low bone density should be incorporated into a treatment algorithm for femoral neck fractures it is essential to make the diagnosis prior to the operation. Due to logistics it would be difficult to assess the bone density of all the hip fracture patients by means of a DXA-scan, because the operation must be performed within 24 hours [162]. Another way to assess the bone density is to use the hip x-ray that was taken to make the diagnosis.

Table 1 Studies of geometrical measures with correlation to BMD, reliability and diagnostic accuracy

Study	N	Test	Correlation BMD	Intrarater reliability	Interrater reliability	Sensitivity / specificity
Hauschild et al [72]	100	SI	0.13-0.29	0.43±0.28[k]	0.20±0.25[k]	0.83/0.24
Patel et al [76]	30*	SI	-		0.80[l]	-
Koot et al [73]	72	SI	-	0.63-0.88[k]	0.08-0.54[k]	-
Smyth et al [80]	25*	SI	0.71-0.79	0.76-0.92#	0.83#	-
Hübsch et al [77]	116	SI	0.79-0.80		0.69-0.77#	-
Bes et al [74]	50	SI	-	0.71[k]	0.71[k]	0.71/0.93
Wachter et al [81]	31	SI	0.73	0.67[k]	0.63[k]	-
Masud et al [79]	659	SI	0.33-0.36	0.64	0.61	0.35/0.90
						0.11/0.97
Dorr et al[85]	52	Dorr	-		5-20 %[v]	
Sah et al [75]	32	SI		88%[α]		
		Dorr		92%[α]		0.85/0.58
		CCR				
		CTI	0.48	96 %[α]		0.62/0.84
Yeung et al [84]	45 *	CBR	0.71	0.97[l]	0.89[l]	-
		CCR	0.34	0.87[l]	0.77[l]	
		CFI	0.46	0.84[l]	0.73[l]	
		MCI	0.60	0.52[l]	0.69[l]	

SI=Singh Index. CCR=canal to calcar ratio. CTI=cortical thickness index. CBR=canal-bone ratio. CFI=canal flare index. MCI=morphological cortical index. *Cadaver studies [k] Kappa statistics [l] ICC #correlation [v]observer variation [α] Unknown statistics

Some of the possible geometrical measures are listed in Table 1 together with the study results, and as mentioned previously, only canal-bone ratio (CBR) has high reliability and correlation. CMR is based on CBR and has also high reliability, but correlation was not used in paper 1 as it was found to be a poor measurement for reliability/agreement [163, 164]. The study by Bes et al [74] seems to have a good reliability and a sensitivity/specificity analysis, but the study is only based on five x-rays. CMR can be used as a screening test for bone density, and in a treatment algorithm it would be valuable to find the patients who have both good bone density and an undisplaced fracture. CMR can exclude low BMD with a positive predictive value of 94 % (CI 80;99) accounting for 25.8 % of the cohort.

Failure and fracture healing

The most important predictor for failure is fracture displacement which greatly influences the failure rate [39, 41, 42, 49, 118, 119, 121-123, 133, 134, 139, 145]. From the Danish Hip Fractures Register report 2011 [3] it is possible to extract the failure rates for the undisplaced fractures (10 %) and the displaced fractures (18 %) treated with IF. The same failure rate is seen for the displaced fractures in paper 3 but in paper 2 the failure rates are 22 % for the undisplaced fracture and 66 % for the displaced fracture. The difference between the two papers lies in the selection of patients as patients who died before the DXA-scan (on average three months after the operation) were excluded. The reason for the different outcomes for the fracture displacement could be the interrupted blood supply to the femoral head after a displaced fracture due to the three-way vascular impact [165, 166]: 1) displacement which interrupts the retinacular vessels; 2) rotation or valgus which interrupts ligament teres vascularisation, and 3) increased intracapsular pressure which produces a tamponade effect. The most important effect here must be the displacement since the retinacular vessels, especially the lateral epiphyseal artery, are responsible for 70-80 % of the blood supply to the femoral head [167, 168]. The damage to the retinacular vessels blood flow caused by the fracture is proportional to the displacement and posterior comminution of the fracture, thereby leading to avascular necrosis [165]. However, the ligament teres artery could supply sufficient blood flow to the femoral head for complete vascularisation[168]. The tamponade effect is probably important for the development of avascular necrosis in the undisplaced fracture because the pressure can get as high as 150 mmHg which may occlude the retinacular arteries. In contrast, segmental collaps of the femoral head is not due to direct cell death but to the repair process originating from the surrounding living bones [169-171].

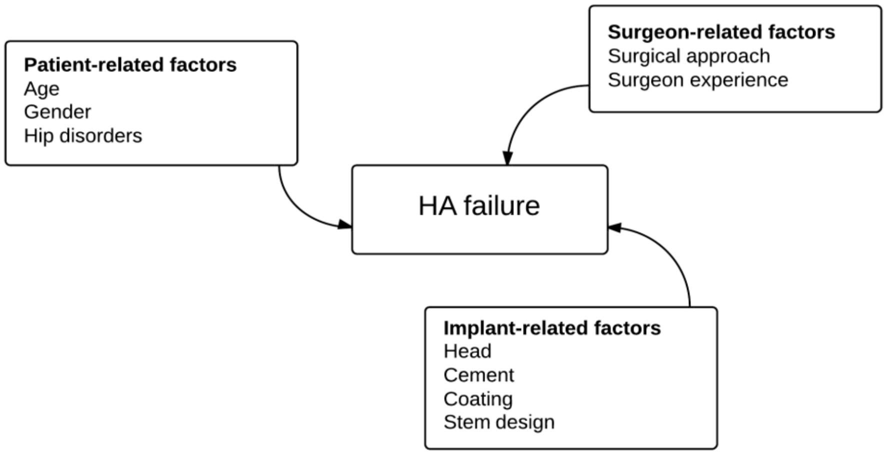
The repair mechanism is the reason for the last fracture healing factor, namely good bone contact. The repair tissue has to cross the fracture line in order to become new bone [165]. The arrest of osteoblast differentiation and of osteogenesis is related to intra-head microfractures blocking the process by inducing mesenchymatous differentiation into fibroblasts forming a fibrous layer similar to that found in non-union [165]. Experimental studies have shown that a major fracture gap can reduce periosteal callus formation and thereby creating impaired ossification [152]. This fits well with the strain theory which states that compressive forces induce fracture healing [172]. This is also the reason for inserting parallel screws, not crossed, thereby allowing maximum compression [173].

Problems in studies of IF failure

Comparisons of studies that evaluate failure predictors for IF are very difficult. One of the main problems is the definition of failure or non-union: some studies use reoperations as an endpoint whereas others use radiographic healing complications (non-union and segmental collaps), and others again use both. As discussed above, reoperations (due to early fixation failure) and radiographic healing complications should be treated separately in the statistical analysis as there are two different pathological reasons for their failures. The statistical analysis is another problem as almost all studies use simple group analysis on each variable instead of statistical methods that evaluate all potential predictors in one analysis, such as the regression analysis or the survival analysis. Use of these methods would enable an evaluation of the magnitude of each confounder, if the studies are large enough. In general, many of the studies evaluating the failure predictors are too small to detect small confounders especially because of the high mortality of the femoral neck fracture patients. The appropriate statistical method to use here would be the survival analysis because it can handle deaths by censoring and a survival sample size calculation with a power of 0.8, a failure rate of 20 %, a hazard ratio of 1.2, and 25 % censoring due to death reveals a sample size of 1718 patients.

Failure and HA

Fig. 3 Elements with influence on HA failure



There is a clear trend towards using HA instead of IF for the displaced femoral neck fracture [2, 4] because of the lower reoperation rates and better functional outcome [29-32]. There are also factors related to an increased risk of failure for HA (Fig. 3) but studies primarily focus on the *implant-related factors*.

Implant-related factors

In Fig. 3 the term head refers to the question of using either a unipolar or bipolar HA. The latest Cochrane review [58] states that there is no evidence of any difference in outcome between bipolar and unipolar prosthesis which is the same conclusion reached by Bhattacharyya and Koval in their review [57]. A recent RCT from Sweden [174] showed no difference in outcome between cemented unipolar and bipolar HA, but a more detailed investigation of the six reoperations (closed reduction not included) revealed that five of them belonged in the bipolar group. The Swedish study also found an increased rate of acetabular erosion after the unipolar HA compared to the bipolar HA, 20 % vs. 5 %. This has been a major concern in the literature on unipolar HA, but in this patient group it is not likely to have an impact on the reoperation rate due to the high mortality rate for this group. Enocson et al [59] investigated 830 femoral neck fractures and were not able to show a difference in reoperation rate between the two HA types. However, a sample size calculation for survival analysis (STATA, stpower cox) on their data (power 0.8, reoperation rate 7 %, hazard ratio 0.8, and estimated censoring due to death 43 %) showed an estimated number of 1262 patients.

In order to answer the question of unipolar vs. bipolar HA, it is necessary to look for register studies that include the sample size required. In the annual report from the Australian Orthopaedic Association National Joint Replacement Registry [175] the cumulative percent revision at eleven years femur is 7.9 % for the unipolar monoblock HA, 8.7 % for the unipolar modular HA at ten years, and 6.4 % at ten years for the bipolar HA. When the report divides the revision by age there is though a lower revision per 100 observation years than for the bipolar HA (Table 2).

Table 2 Cumulative percent revision by age and stem from the Australian annual report

Revision	< 75 years	75-84 years	≥ 85 years
Unipolar monoblock			
N total	1996	8767	11584
1 year revision	4.5 %	3.3 %	2.4 %
5 years revision	13.8 %	6.6 %	3.5 %
Revision/100 obs yrs	1.19 (0.99;1.41)	0.76 (0.63;0.90)	0.81 (0.64;1.02)
Unipolar modular			
N total	3372	7493	7056
1 year revision	2.6 %	2.1 %	1.4 %
5 years revision	9.2 %	4.8 %	2.0 %
Revision/100 obs yrs	2.14 (1.86;2.45)	1.20 (1.05;1.37)	0.81 (0.66;0.98)
Bipolar			
N total	2364	4538	3473
1 year revision	2.6 %	1.9 %	1.9 %
5 years revision	6.1 %	3.6 %	3.0 %
Revision/100 obs yrs	2.87 (2.47;3.32)	1.62 (1.46;1.79)	1.10 (0.97;1.24)

An important confounder is the use of cement or not which is not adjusted for. A study from the Swedish Hip Arthroplasty Register [176] shows a higher reoperation rate for unipolar uncemented HA (6.7 %) compared to unipolar cemented HA (2.4 %) and bipolar HA (3.5 %). After adjusting for age, gender, side, reason for surgery, surgical approach, and type of hospital the risk of re-operation is increased for the unipolar monoblock HA (2.0; CI 1.5–2.8). The use of cemented monoblock HA did not influence the risk of re-operation compared to modular implants (0.7;CI 0.5–1.2). However, a different study also using data from the Swedish Hip Arthroplasty Register [177] finds that the bipolar HA has an increased overall revision rate (3.5 %) compared to the unipolar HA (2.5 %). This gives a hazard ratio of 1.3 after adjusting for age, sex, diagnosis (primary or secondary), type of stem (cemented or uncemented) and surgical approach. Even though adjusting for type of stem, a confounder could lie in the patients receiving the unipolar stem. If it is only for the elderly and fragile patient then they would have an increased mortality and therefore not have the same revision rate. Thus, there is no clear evidence for difference in failure for unipolar HA compared to bipolar HA.

Cementing

Regarding cemented vs. uncemented HA treatments in RCTs, the reoperation rates are comparable [58, 178-180], but there is a major problem concerning the follow-up time. Paper 3 shows significantly lower reoperation rate for cemented HA compared to uncemented HA, and according to the Kaplan-Meier curve (Fig. 2 in paper 3) a large difference does not occur until after 3-4 years. This means that a fairly large sample size is required to detect a small difference after 1-2 years as also seen in the RCTs. Three RCTs had a follow-up time longer than five years [64-66]. Ravikumar et al [65] had 13 years of follow-up and reported a reoperation rate for the uncemented HA of 24 % compared to 11 % in paper 3. The uncemented HA was in both cases the Austin-Moore stem which is known for its inferior outcome in other study types[181]. Parker et al [66] had a follow-up time of 9-15 years, and they also used an Austin-Moore stem which had a reoperation rate of 7 %. The difference in the reoperation rates between the study by Parker et al [66] and paper 3 could be a consequence of the nationwide search for reoperations through the national registries of patients. Leonardsson et al [64] had 10 years follow-up time in a multicenter RCT and therefore a different implant was used. The Austin-Moore stem had significantly higher reoperation rate (23.5 %) compared to the cemented Lubinus Variocopf (1.9 %) and Charnley-Hastings (7.1 %). In comparison, paper 3 had a reoperation rate of 5.3 % for the cemented Charnley-Hastings HA. The Australian Orthopaedic Association National Joint Replacement Registry [175] also shows a higher reoperation rate for the uncemented HA compared to the cemented HA and a major difference seems to occur after approximately three years.

Coating

Today the data for these older types of uncemented HA are more of historical interest because the Austin-Moore HA is almost phased out in the Scandinavian countries [2, 176]. The more modern types of uncemented HA are hydroxy-apatite coated and there is only one RCT [182] comparing an older uncemented HA (Austin-Moore) with the modern uncemented hydroxy-apatite coated HA (Furlong), and this study found no significant difference in outcome after one year. The problem may be that this study used the Furlong stem which was also used in Paper 3 and which also found comparable reoperation rates compared to the Austin-Moore stem. The reoperation rates were relatively high in both studies after 12-19 years follow-up compared to the cemented HA. One RCT compared a cemented HA with an uncemented hydroxy-apatite coated HA [61]. The study found no difference in the reoperation rates after one year (7.4 % in the uncemented group vs. 6.3 % in the cemented group) which in agreement with the findings in paper 3 after one year (12/157 = 7.6 %). However, paper 3 showed that 52 % of the reoperations occur after one year with a total of 15.9 % for the uncemented hydroxy-apatite coated HA. A newly published study from the Norwegian Hip Fracture Register [62] showed a five year survival of 97 % for the cemented HA which is statistically higher compared to 91 % for all uncemented HA which were almost exclusively hydroxy-apatite coated HA (Corail). This long term difference between cemented and uncemented HA is consistent with the findings in paper 3.

Stem designs

There are some stem designs for HA, such as the Austin-Moore stem, which increases the risk of failure. In the annual report from the Australian Ortheopaedic Association National Joint Replacement Registry there are investigations of uncemented prostheses with higher rates of revision than anticipated [183]. It is important to acknowledge that some stem types may not be appropriate for the femoral neck fracture patients compared to the arthroses patients because of the differences between the two patient groups. One difference in particular is osteoporosis which must be taken into account when using an uncemented stem as this leads to more intraoperative fractures and accompanying subsidence compared to treatment with cemented HA [61, 180, 184, 185].

Surgeon-related factors

The surgeon has several approaches to hip to choose from when performing alloplasty surgery: The anterior, anterolateral, direct lateral/transgluteal, lateral transtrochanteric, posterior/posterolateral, and minimal invasive approach [186]. A Cochrane review updated in 2009 found only one RCT comparing surgical approaches for inserting hemiarthroplasty of the hip and the review found insufficient evidence to determine a optimum surgical approach [187]. A few years later a paper by one of the same authors reviewed all evidence levels for dislocation risk factors and found that the posterior approach was associated with an increased risk for dislocation [188]. Since then 6 papers has been published regarding the surgical approach and HA [177, 189-193]. The first study compared two surgical periods during which the surgeons changed the approach from posterolateral to anterolateral [193]. The study included 372 patients but only half of the patients were treated with HA (the other half were treated with THA). In the anterolateral group there were 1 revision compared to 2 revision for the primary HA's. Another study compared the posterior and transgluteal approach and showed 3.9 % dislocation rate for the posterior approach and 0.5 % for the transgluteal approach but there was no difference in the overall reoperation rate [189]. Two studies [190, 191] compared the anterolateral and posterior approach and found 5-13 % dislocation in the posterior approach group and 0-3 % in the anterior approach group. However, the studies only look at the dislocation rate and not the overall reoperation rate. One study looked at 1812 patients with primary HA and 74 % of them were femoral neck fractures [192]. The study used the anterolateral approach (79 %), posterolateral (14 %), and transtrochanteric (7 %) and there were no difference in the dislocation rate. There were, however, a higher revision rate for the transtrochanteric approach (3.2 %) than for the anterolateral (1.0 %) or posterolateral approach (0.8 %) but this could be a type 1 error due to the low number of dislocations in the groups. The by far largest study [177] with 23,509 procedures uses data from the Swedish Hip Arthroplasty Register and it shows that the posterior approach has a 3.4 % dislocation rate and the anterolateral approach has 2.8 %. This gives a hazard ratio of 0.72 for dislocation when using the posterior approach but when including all reoperation reasons there is no difference between the anterolateral and the posterior approach. Even though dislocation is higher for the posterior approach and one of the main reasons for reoperation in Sweden (73 %) [4], Norway (minimum 30 %) [2], and Australia (11-20 %) [175] there does not seem to be any difference in the overall reoperation rate between the surgical approaches to the hip.

There is a learning curve for inserting HA and it seems to be steeper than for IF [142]. For THA this learning curve results in more reoperations due to inexperience [194] but this does not seem to be a major issue for HA. There are very few studies that include surgeon experience in their assessment of reasons for failure after HA. Enocson et al. [190] found no difference between the dislocation rate between registrar and post-registrar surgeons but the 75 % of the registrar used the anterolateral approach compared 55 % of the post-registrar and there was only 8 dislocations in registrar group. Schliemann et al. [195] found a higher complication rate in the less experienced group (9.6 %) compared to the experienced group (6.3 %) but it was not statistical significant. The less experienced surgeons operations were supervised and a strictly failure rate cannot be extrapolated. The by far largest study was from an insurance cohort and included 115,352 patients [196]. There was a lower dislocation rate (1.2 % vs. 1.7 %) and superficial infection (1.1 % vs. 1.6 %) amongst high volume surgeons compared to low volume surgeons. There was, however, a higher revision rate in the high volume group which could be due to an increased surveillance for radiographic abnormalities such as acetabular erosion and femoral stem loosening in the high volume group. Therefore there do not seem to be major difference in failure rate between less experienced and experienced surgeons for HA.

Patient-related factors

There seems to be a decreasing risk of failure with increasing age which is the opposite of the relation between IF and age. This is demonstrated in the Australian Orthopaedic Association National Joint Replacement Registry [175] which holds information from graphs and tables of the cumulative revision percentages of primay unipolar monoblock HA, unipolar modular HA, and bipolar HA by age (table 2). There is a difference of 0.32 revisions per 100 observation years between patients younger than 75 years and patients older than 84 years for unipolar monoblock HA, 1.33 for unipolar modular HA, and 1.77 for bipolar HA. A study from the Swedish Hip Arthroplasty Register [177] shows the same results with a revision rate of 5.6 % in patients below 75 years (hazard ratio 1.8), 3.2 % in patients between 75-85 years (hazard ratio 1.2), and 2.4 % in patients above 85 years.

There also seem to be an increased risk of failure for men compared to women. The annual report from Australia [175] shows a hazard ratio of 1.3 for revision in men after adjusting for age in bipolar HA for the entire period. There is a similar trend for the unipolar monoblock and modular HA's but it is not statistical significant. However, looking at the revision per 100 observation years in table 3 there seems to a statistical significant difference for all HA's.

Leonardsson et al [177] finds a hazard ratio of 1.2 for revision in men after adjusting for sex, diagnosis (primary or secondary), type of stem (cemented or uncemented), type of head (bipolar or unipolar), and surgical approach.

Table 3 Cumulative percent revision by gender and stem from the Australian annual report

Revision	Male	Female
Unipolar monoblock		
N total	5875	16472
1 year revision	3.6 %	2.8 %
5 years revision	7.2 %	5.8 %
Revision/100 obs yrs	2.05 (1.77;2.35)	1.42 (1.31;1.53)
Unipolar modular		
N total	4924	12997
1 year revision	2.5 %	1.7 %
5 years revision	6.1 %	4.8 %
Revision/100 obs yrs	1.76 (1.50;2.05)	1.17 (1.06;1.30)
Bipolar		
N total	7856	7638
1 year revision	2.4 %	2.0 %
5 years revision	5.4 %	3.7 %
Revision/100 obs yrs	1.18 (0.96;1.45)	0.82 (0.72;0.93)

Another patient-related factor that could make HA less feasible is hip disorders, such as anatomical abnormalities (i.e. dysplasia which increases the risk of dislocations) and degenerative alterations (i.e. arthrosis which increases the risk of secondary operation due to pain).

Conclusion

Both the literature review and thesis study finds that IF failure occurs primarily within the first two years and the most important predictors seem to be fracture displacement, implant positioning, quality of reduction and age. Other predictors with minor importance are gender, surgeon experience, time to surgery and implant design. Paper 2 finds that bone density is of minor importance, if any, regarding risk of failure but might play a larger role of failure in the undisplaced fracture. The literature shows that blood supply is important for fracture healing and is probably responsible for the major part of avascular necrosis. For failure of HA there is no difference when comparing unipolar with bipolar HA when reviewing the literature. Paper 3 and the literature shows that there is a higher failure rate for older uncemented HA compared to cemented HA, especially after 5-10 years. Paper 3 also finds that the uncemented HA does not seem to benefit from hydroxy-apatite coating when comparing the failure rates of uncemented HA to those of the cemented HA. The long term failure rates of uncemented HA is a matter of concern, and cemented HA should be the first choice in the treatment of the displaced femoral neck fractures. Other predictors for increased risk of failure concerning HA are age and uncemented stem designs according to the literature in contrast to the surgical approach and surgeon experience which does not seem to increased the risk for failure. From the literature it is shown that many of the geometrical measures on x-rays are not reliable and correlate poorly with BMD. Paper 1 show that CMR is a reliable measure and can assess the bone density in 38 % of the cohort.

In general, the studies assessing the failure risk are not large enough, and the appropriate statistics should be the survival analysis.

Perspectives

In order to assess failure predictors for patients with femoral neck fractures it is important to make an appropriate sample size calculation taking the high mortality rate into account. Therefore there is a need for larger well-conducted studies which take known failure predictors into account. Implant positioning seems to play an important role in failure and scoring systems for the clinical use need reproducibility and validity studies. Close attention to national registries should be made for the next couple of years when the survival rates of the uncemented HA have been determined.

The impact of bone density on risk of failure for the undisplaced fracture should be investigated using DXA scan. CMR could be used as a screening test for good bone density but needs to be studied further.

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Paper 1

Cortical Marrow Ratio: A revised method to detect or exclude low bone mineral density in plain x-rays of the hip

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Abstract

Backgroud: The use of x-rays for detecting low bone density has yet to be proven valid. The purpose of this study was to evaluate the applicability of cortical marrow ratio (CMR) in terms of reliability and diagnostic accuracy for bone mineral density (BMD) levels.

Method: A total of 132 consecutive femoral neck fracture patients (median age 81.2 years, inter-quartile range 70.6-86.1) from a prospective cohort were assessed with dual energy x-ray absorptiometry (DXA) scans and digital hip x-rays. CMR was measured twice by two independent observers and analysed for reliability. CMR was then compared to BMD by means of a diagnostic precision analysis.

Results: Using total hip BMD, 47 patients were found to have a T-score ≤ -2.5 with a median (inter quartile range - IQR) CMR of 1.61(IQR 1.44-1.74), and 85 patients were found to have a T-score > -2.5 with a median CMR of 1.89 (IQR 1.77-2.11). When measured using the intraclass correlation coefficient (ICC) reliability parameter, the intra-rater reliability was 0.98 and 0.87, and the inter-rater reliability was 0.86. A receiver operating characteristic (ROC) analysis resulted in two optimal cut-off threshold values for the CMR measurements with positive predictive values (95 % CI) for finding low BMD of 81 % (54;96) and for excluding low BMD of 94 % (80;99).

Conclusion: CMR was found to be a reliable measure to detect or exclude low hip BMD for 37.9 % of the cohort.

Keywords: reliability, BMD, femoral neck fracture, x-ray, sensitivity.

Introduction

Hip fracture is a worldwide challenge particularly in the developed countries [1, 2]. Despite the signs of decreasing incidence there is an increase in the overall number of hip fracture patients in northern Europe [3-5]. For surgical treated femoral neck fractures this will potentially lead to a higher failure rate which for internal fixation is approximately 35 % in dislocated fractures [6, 7]. Predictors for failure should therefore be investigated and made feasible to implement in clinical practise.

One possible predictor for failure osteosynthesis is osteoporosis. Low BMD is a well-defined risk factor for hip fracture [8] and experimentally, several studies have shown that low BMD affects the strength of osteosynthesis [9-11]. DXA scan has been recognized as the gold standard for diagnosing osteoporosis [12]. However, in a clinical setting it can be logistically very difficult to obtain a DXA scan before surgery and due to surgical delay it may even increase the in-hospital mortality for hip fracture patients [13, 14].

A fast and feasible way to estimate low BMD is to use the existing x-ray image used for diagnosing the fracture. The Singh Index [15] is the oldest and best known geometric measure for osteoporosis, but the Singh Index' reliability is either poor [16, 17] or acceptable [18-20]. The major drawback of most studies using the Singh index is, however, that they only show poor to moderate correlation with BMD [16, 17, 19, 21-25]. Several other geometrical measures have been suggested [19, 22, 26-30]. Of these, the canal bone ratio, the cortical thickness index, and the Dorr classification have shown good reliability by having an ICC above 0.8, but only canal bone ratio had a correlation with BMD above 0.7. However, the correlation coefficient looks at the degree of association, not the agreement as stated by Bland and Altman [31]. Thus, high correlation does not imply close agreement because the correlation coefficient is blind to the possibility of bias.

The canal bone ratio study [28] is on cadavers and uses a fixed measurement point which does not account for the morphological differences of small and large femora. In order to take account for the variability of femoral geometry CMR was developed. The purpose of this study is to evaluate the applicability of CMR in terms of reliability and diagnostic accuracy for BMD levels.

Patients and Methods

Subjects

Data was retrieved from a prospective consecutive cohort of patients with hip fractures [32], which included all hip fracture patients who were older than 45 years and were treated at the Department of Orthopaedic Surgery and Traumatology, Odense University Hospital between 01.01.2005 and 31.12.2006. The study [32] was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and approved by the Danish Data Protection Board (J.nr. 2010-41-5194). The exclusion criteria were:

- Cognitive impairment: the patient could not understand the information given by the enrolling person
- Serious illness: the enrolling person assessed whether the patient could benefit from osteoporosis treatment, i.e. sufficient length of expected survival to experience treatment effect.
- High energy fracture
- Pathological fracture

A total of 450 consecutive femoral neck fracture patients were treated and eligible for a DXA-scan (Fig. 1). 277 patients were excluded mainly due to cognitive impairment, severe illness, or unwillingness to participate. 158 femoral neck fracture patients with DXA-scans had their x-rays assessed. One patient was excluded due to an old fracture, three patients due to transferrals and 22 patients were excluded due to the femoral portion for measurement was not included. This left a total of 132 patients with femoral neck fracture and DXA-scans, who comprised the final study cohort. The median time from operation to the DXA-scan was 80 days (IQR 42-142). All x-ray images from the cohort were evaluated to ensure correct fracture diagnosis. Any discrepancies in diagnosis were discussed and resolved.

Measurements

Preoperative x-rays of the patients in the final cohort were used. Based on a pilot study of 20 patients, the CMR was assessed by the following method:

1. A circle was drawn just below the lesser trochanter containing the femoral diameter. A second circle was drawn approximately two femoral diameters below the first circle. A line was drawn based on the centers of the two circles depicting the midline (Fig. 2a).

2. The circles were removed and a new line perpendicular to the midline was drawn placed at the crossing point between the dense trabecular structure of the lesser trochanter and the cortex below (Fig. 2b). The length of the line was then set to the width of the femur.

3. A new line was placed perpendicular to the midline 2 x distal (x = length of first line) to the first perpendicular line, and at this line the femoral cortical and marrow diameter was measured (a and b in Fig. 2c).

CMR = femoral diameter / marrow diameter = a / b

Two independent observers analysed all x-rays twice (approximately 12 weeks apart) to obtain inter- and intra-rater reliability and agreement. Rater 1 was an orthopaedic resident and rater 2 was a radiology resident. Measurements were also carried out on postoperative x-rays to assess whether the CMR was affected by external rotation of the femur on the pre-operative x-rays. For the purpose of inter-rater reliability and agreement, the first measurement of both raters was used. The BMD from the DXA-scans were compared to the first measurements of rater 1. The DXA-scanner was a Hologic Discovery and NHANES III was used as reference material [33]. Low BMD level using total hip BMD was defined as a T-score ≤ -2.5 [34]. All x-rays were digital and measurements were carried out on a 21-inch screen or larger using Sectra AB's RIS/PACS x-ray viewing system.
The raters were blinded to each other's measurements and BMD results, which were merged with the CMR results after completion of the second CMR measurements.

Statistical analysis

The statistical software programme STATA 11 was used for the analyses. Reliability is in this context defined by de Vet et al. [35] and based on the $ICC_{agreement}$ reliability parameter. Inter-rater agreement was expressed by the agreement parameters Limits of Agreement, and $SEM_{agreement}$ (Standard Error of Measurement). To calculate $ICC_{agreement}$, Limits of Agreement and $SEM_{agreement}$ a multilevel mixed-effects linear regression technique was applied. For a graphical estimate of systematically bias and agreement, a software extension (SJ7-3: st0015_4) for STATA was downloaded to give the Bland-Altman plot. A diagnostic precision analysis (extension SJ-4-4: sbe36_2) was applied to evaluate CMR for assessment of low BMD. ROC analysis was used to find optimal cut-off thresholds of over 95 % sensitivity and specificity. The correlation coefficient was calculated to compare to other studies. Stability assessment of CMR from preoperative to postoperative x-rays was analysed using the Wilcoxon matched-pairs signed-ranks test.

A retrospective power analysis for the reproducibility study using STATA' sampicc extension was done with a hypothesized ICC value of 0.9 and a null value of 0.8, which gives a power of 100 %. A post-hoc analysis on the sample size of the diagnostic precision analysis using precision 0.05, prevalence 0.36, and specificity = 0.96 gave a sample size of 92 [36]. If the calculations were based on sensitivity = 0.96, precision 0.05, and prevalence 0.36, the sample size was 164.
The reporting of this article is done according to both GRASS and STARD guidelines [37, 38].

Results

X-ray images were included for 132 patients (32 men and 100 women), median (IQR) 81.2 (70.6-86.1) years, and no age difference between the sexes (Wilcoxon rank-sum test: $p<0.68$).

The CMR measurements were median (IQR) 1.81 (1.58-2.01) and 1.81 (1.58-1.97) for rater 1 with an intra-rater mean difference of 0.009. For rater 2 the CMR measurements were median 1.82 (1.60-1.99) and 1.84 (1.63-2.01) with an intra-rater mean difference of -0.05. The calculated reliability parameter ICC (95 % confidence interval (CI)) gave an intra-rater $ICC_{agreement}$ of 0.98 (0.97;0.99) for rater 1 and of 0.87 (0.83;0.91) for rater 2. The inter-rater mean difference was 0.021 and $ICC_{agreement}$ was 0.86 (0.81;0.90). Agreement parameters were Limits of Agreement (-0.28 – 0.32) and $SEM_{agreement}$ 0.11. No systematic difference (bias) between the raters were found, but there was an intra-rater difference for rater 2 of 0.05 ($p<0.001$, multilevel mixed-effects linear regression). A Bland-Altman plot was applied to the data, and there was a uniform distribution of the differences for the whole range of the CMR values.

A total of 47 patients (35.6 %) were found to have low BMD levels using total hip BMD with a median (IQR) BMD of 0.57 (0.50-0.61) (Table 1). The ROC-analysis resulted in two optimal cut-off threshold values for the CMR measurements, one at 1.45 to find patients with low BMD and another at 2.0 to exclude patients with low BMD. Based on these cut-off values the positive predictive value (95 % CI) for finding low BMD was 81 % (54;96) and for excluding low BMD, 94 % (80;99) (Table 2). This is graphical displayed in figure 3 and the correlation coefficient for CMR and total hip t-score was $r=0.55$. CMR used as a screening test can find or exclude patients with low BMD for 37.9 % of the cohort with high predictive values. At case level this would lead to incorrect status assessment for 5 out of 50 patients. A total of 63 patients (47.7 %) were found to have low BMD levels using total hip and spine BMD. CMR could with a positive predictive value of 82 % (57;96 – 12.9 % of the cohort) find low BMD patients or exclude low BMD patients with a value of 84 % (60;97 –14.4 % of the cohort). The correlation coefficient was $r=0.62$.

Based on 74 postoperative x-rays, the median (interquartile range) difference between preoperative and postoperative CMR measurements was 0.19 (0.03;0.41). There was a statistically significant difference between rater 1's first measurement ($p<0.001$, Wilcoxon matched-pairs signed-ranks test) and the postoperative measurements. Based on postoperative x-rays, finding or excluding low BMD could be done for 46.0 % of the cohort (calculated as shown in Table 2). Of the 292 excluded patients, 50 were randomly selected for CMR measurement. For 16.7 % of this cohort, CMR was below 1.45 and for 11.9 %, CMR was above 2.0.

Discussion

CMR has excellent intra- and inter-rater results and is therefore reliable. Diagnostic precision expressed as positive predictive values were very high for excluding low BMD at the hip (94 %) and somewhat lower for finding low BMD (81 %). Therefore, CMR with the specified thresholds can detect or exclude low BMD for 37.9 % of the cohort based on preoperative x-rays. For a subsample with available postoperative x-rays, the corresponding percentage is 46 %.

Conceptually, the reliability expresses the ability to distinguish between patients, despite measurement errors. The reliability is therefore a characteristic of the performance of an instrument (CMR) and CMR is used for discriminative purposes [35]. $ICC_{agreement}$ takes the systematic difference between the measurements into account and is therefore used as the reliability parameter. This study showed excellent reliability with an inter- and intrarater ICC of 0.86-0.98 which only has been shown in one other paper [28]. It is not possible to use an agreement parameter such as the Bland-Altman plot because the BMD (range 0.4-1.1) and the CMR (1.3-2.8) results are not on the same scale. The correlation coefficient was 0.55 but should be interpreted with caution because high correlation does not imply close agreement since the correlation coefficient is blind to the possibility of bias [31]. Instead, a diagnostic precision analysis was applied for evaluation of classification of osteoporotic status.

Sensitivity and specificity analyses of geometrical measures compared to BMD measurements have been carried out in four studies using the Singh Index, the Dorr classification, the canal-to-calcar ratio, and the cortical thickness index [16, 18, 19, 23]. Bes et al. [18] showed high sensitivity of 71 % and specificity of 93 % for the Singh Index but only has 5 patients in that analysis. The other studies using the Singh Index [16, 23] are larger (n=100 and 659) but have either low sensitivity or specificity. The only study with other measurements than the Singh Index is Sah et al. [19] and it showed sensitivity ranging from 62-85 % and specificity 58-84 % for the cortical thickness index and the Dorr classification. Even though it has interesting results the study has a low number of participants (n=32) and the risk for a type 2 error is quite large. The present study have high sensitivity and specificity but also uses two cut-off values for the diagnostic precision analysis and can therefore not be compared with the above mentioned studies.

In a potential, clinical setting CMR can be used to assess whether patients should be further examined, low BMD or not. For optimal classification of BMD level, high specificity must be ensured to avoid false positive results and high sensitivity to avoid false negative results. But in terms of diagnostic precision for the individual patient, the positive predictive value is more important. With the suggested two cut-off points for the CMR score and comparisons to DXA scans, the results indicate that CMR score can both exclude low

BMD (positive predictive value of 96 %) and find low BMD (positive predictive value 81 %). In total, excluding or finding low BMD can be done for 37.9 % of the cohort. With regard to number of patients, this would in the current study have led to 3 patients out of 16 with false positive results and 2 patients out of 34 with false negative results compared with the results based on DXA scan.

The following limitations are noted: a slight underpowering shown in the post-hoc analysis, and 14 % of the routine x-rays excluded due to insufficient femoral shaft length used for CMR measurement on the x-rays. There is a small systematic bias in the repeated measurement by rater 2, possibly due to the application of a different zooming level on the second measurement. In further studies specification of zooming should be specified for reading the digital x-rays. Although this is a population-based study with a well-defined cohort, it is also very selective. Patients with severe co-morbidity and dementia were excluded and this is reflected by the lower CMR measurements in the patients excluded from this study. This group would, according to the exclusion criteria, therefore not benefit from osteoporosis treatment.

The postoperative x-rays produced similar diagnostic results as the preoperative, but interestingly, CMR could detect or exclude low BMD for 46.0 % of the total postoperative cohort compared to 37.9 % of the preoperative cohort. The median pre- and postoperative difference in CMR was only 0.19 due to the rotation of the femur while fractured. This could indicate that assessment of CMR has stronger correlation with BMD when the femur is in a neutral position and therefore the un-fractured hip should be measured instead, but further analyses are needed. The higher classification percentage is most likely unbiased, since half of the 58 dropouts (132-74) were transferred for surgery to another hospital due to lack of resources and the other half had x-ray images which did not include the portion of the femur for CMR measurement.

For hip fracture patients, an important risk factor is decreased BMD, and there is an increased risk for a new hip fracture within the first 12 months after the first hip fracture [39]. Although there seems to be effective medicine preventing new fractures in this time period [40], the high mortality rates of hip fracture patients must be taken into account [41]. CMR might, perhaps in combination with other parameters, be used as an assessment of low BMD at the hip in the future hip fracture patients. In patients with BMD determind in the spine and hip, CMR excludes osteoporosis in at least 14 % of the femoral neck fracture patients and thereby reducing referrals for DXA-scan as well as the radiation burden.

In conclusion, CMR was found to be a reliable measure of detecting or excluding low BMD, but further investigation of the CMR method is needed.

Conflict of Interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article

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Figures

Fig. 1 Flowchart of patient enrolment

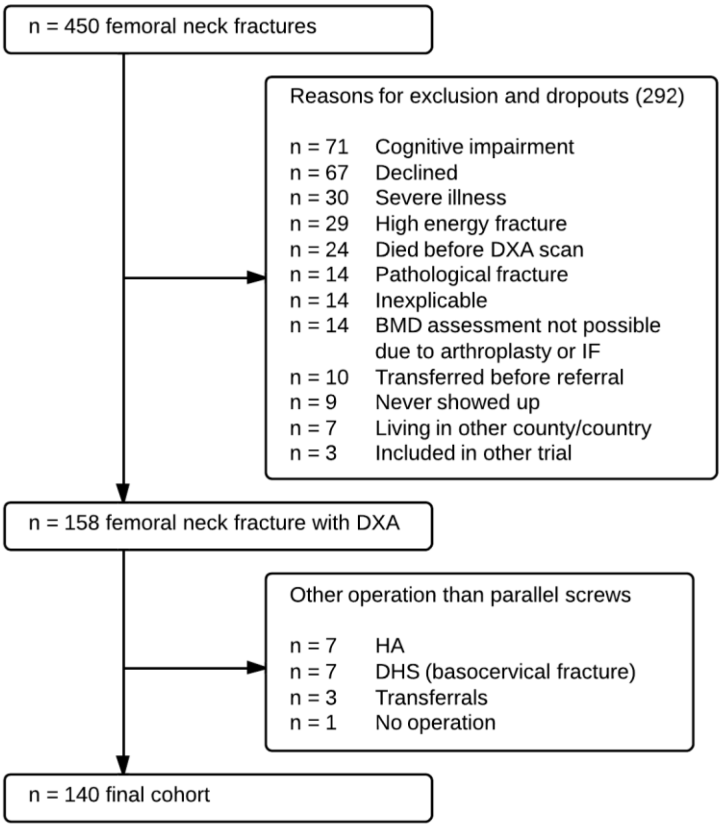
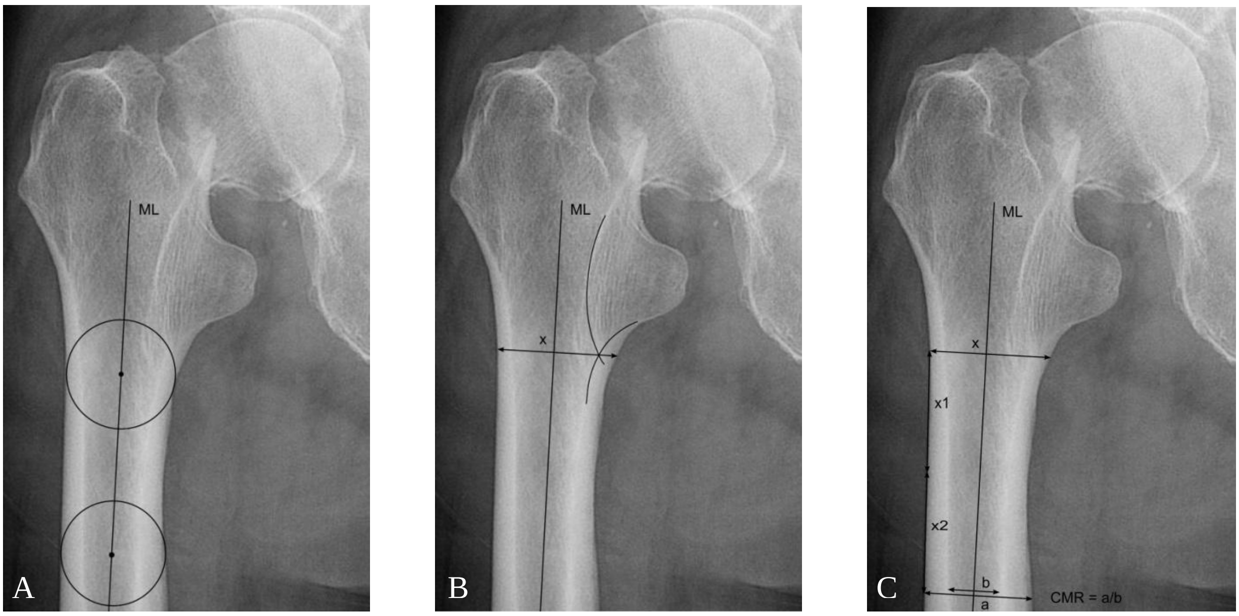


Fig. 2A CMR measurement, step one **Fig. 2B** CMR measurement, step two **Fig. 2B** CMR measurement, step three

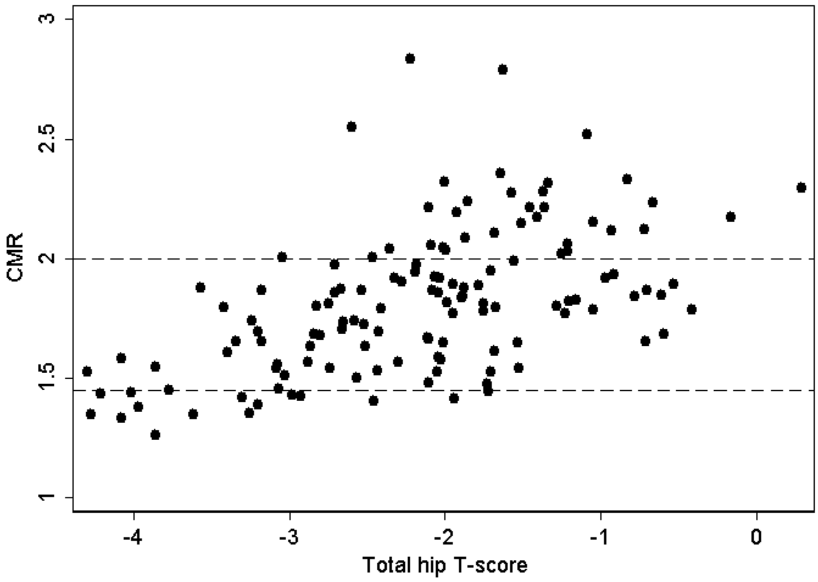


ML = midline

x = femoral diameter

a = outer cortex, b = inner cortex, x1 and x2 = x in length

Fig. 3 Scatter plot of CMR and total hip t-score



Tables

Table 1 Study population by total hip BMD status

Total hip BMD	T-score ≤ -2.5	T-score > -2.5
Number of patients	47	85
BMD (IQR)	0.57 (0.50-0.61)	0.74 (0.70-0.81)
CMR (IQR)	1.61 (1.44-1.74)	1.89 (1.77-2.11)
Age (IQR)	82.8 (75.9-87.2)	80.0 (69.6-84.9)
Gender (male/female)	4/43	28/57

Table 2 Diagnostic precision based on CMR values and total hip BMD

CMR		T-score ≤ -2.5	T-score > -2.5
Low threshold (find low BMD)			
Low BMD	(CMR < 1.45)	13	3
Not low BMD	(CMR > 1.45)	34	82
PPV*=81 (54;96), SP¤=96 (90;99), percentage diagnosed: 12.1 %			
High threshold (exclude low BMD)			
Low BMD	(CMR < 2.0)	45	53
Not low BMD	(CMR > 2.0)	2	32
PPV*=94 (80;99), SP¤=96 (86;100), percentage diagnosed: 25.8 %			

*Positive Predictive Value with 95 % confidence interval
¤Specificity with 95 % confidence interval

Paper 2

Bone density in relation to failure in femoral neck fracture patients treated with internal fixation

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Abstract

Background: Internal fixation (IF) in femoral neck fractures has high reoperation rates and finding predictors for failure is an ongoing process.

Purpose: examine BMD in regard to failure of femoral neck fractures in patients treated with IF.

Methods: 140 consecutive patients (105 females, 35 males, median (interquartile range - IQR) age 80.1 (70.3; 84.9)) treated with IF had a dual-energy x-ray absorptiometry (DXA) scan performed. Their x-rays were evaluated for fracture displacement, implant positioning, and quality of reduction. From a questionnaire performed during admission two variables for co-morbidity and walking disability were chosen. Information on operation date, reoperation, and death were retrieved from the region based Patient Administrative System and The National Registry of Patients at the end of 2010. Primary outcome was BMD compared to hip failure (resection, arthroplasty, or new hip fracture). A Cox regression model was applied and adjusted for age, gender, quality of reduction, co-morbidity and walking disability.

Results: 49 patients had a t-score below -2,5 SD and 70 patients had a failure. The failure rate after two years was 22 % (95 % CI 12;39) for the undisplaced fractures and 66 % (95 % CI 56;76) for the displaced fractures. The Cox regression showed no association of low hip BMD (hazard ratio 0.82 (95 % CI 0.46;1.47), p=0.506) and failure. For the covariate only implant positioning (hazard ratio 65.8 (95 % CI 3.5;1240.4), p=0.005) showed an association with failure.

Conclusions: Low hip BMD is not associated with fixation failure in femoral neck fracture patients treated with IF.

Keywords: Internal fixation, femoral neck fracture, failure, BMD, osteoporosis, implant positioning, quality of reduction

Introduction

Internal fixation (IF) for the femoral neck fracture has many advantages such as minimal blood loss, short operating time and low infection rate [1]. The trend is, however, to do more hemiarthroplasties in displaced fractures [2] partly due to a high re-operation rate of IF in comparison to arthroplasty (40 % versus 11 %; risk ratio 3.22) but also due to better functional outcome [3, 4]. The high reoperation rate is mainly due to early fixation failure and to lower re-operation rates after IF it is mandatory to know failure predictors.

Possible fixation failure predictors can be grouped into the following four categories: *patient-related factors* are age and gender: there seem to be an increased risk of non-union with older age [5-7] but the literature with large studies is not so clear regarding gender because two studies finds an association for female having increased risk of failure [5, 8] and two other studies do not [7, 9]. *Surgeon-related factors* are quality of reduction and implant positioning: poor reduction results in higher non-union rates [10-12] and inferior placed IF are reported to lead to higher failure rates [10, 13]. There do not seem to be any *implant-related factors* contributing to fixation failure [14, 15]. *Fracture healing* is determined by three ideal conditions: adequate blood supply, good contact between bone fragments and good stability [16]. The most important factor is bone contact as there are lower re-operation rates for undisplaced (11 %) than displaced fractures (40 %) [3, 17].

Moreover, bone quality expressed as bone mineral density (BMD) might be an important predictor for failure. BMD is a well-defined risk factor for hip fracture [18] and experimentally, several studies have shown that BMD affects the strength of osteosynthesis [19-21] in addition to delayed fracture healing [22, 23]. However, it is debated how osteoporosis affects fracture fixation and healing has clinically [23, 24].

The aim of this study is to evaluate the effects of low BMD on failure of internal fixed femoral neck fractures.

Patients and methods

Patients

Data was retrieved from a prospective consecutive cohort of patients with hip fractures [25], which included all hip fracture patients who were older than 45 years and were treated at the Department of Orthopaedic Surgery and Traumatology, Odense University Hospital between 01.01.2005 and 31.12.2006. The study [25] was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans and approved by the Danish Data Protection Board (J.nr. 2010-41-5194). The exclusion criteria were:

- Cognitive impairment: the patient could not understand the information given by the enrolling person
- Serious illness: the enrolling person assessed if the patient could benefit of osteoporosis treatment i.e. sufficient length of expected survival to experience treatment effect.
- High energy fracture
- Pathological fracture

A total of 450 consecutive femoral neck fracture patients were treated and therefore eligible for a DXA-scan. 292 patients were excluded/dropped mainly due to cognitive impairment, severe illness, or declined to participate. 158 femoral neck fracture patients with DXA-scan had their x-rays assessed. 18 patients were treated with another implant than standard IF (Uppsala screws) therefore the final cohort consisted of 140 patients (fig. 1).

All x-rays from the cohort were evaluated by the first author to ensure correct fracture diagnosis. Any discrepancy was discussed with at least one of the other authors and consensus was achieved. In table 1 the key patient demographics are listed according to failure.

Data for follow-up

Information on operation date, reoperation, death, and operations type (if x-ray not available) were retrieved from the County based Patient Administrative System. All patients were treated with closed reduction and IF using two Uppsala screws which was the treatment of choice at that time for all femoral neck fractures regardless of fracture displacement or age of patient. All patients were primarily operated or supervised by a senior registrar. Postoperatively, full weight bearing exercises from day 1 were encouraged and similar drugs for thrombosis prophylaxis and antibiotics were given. Failure defined as any reoperation that leads to major reoperation with change of IF (resection, arthroplasty, or new hip fracture), simple removal of IF was not included. 68 patients had failure and by extracting the same data from The National Registry of Patients (NRP), 2 more patients with reoperations in another county was located. The search in NRP included all diagnosis and procedures that may have lead to loss of hip implant or new hip fracture.

BMD

During admission a questionnaire was conducted and patients were referred for a DXA-scan. The contralateral hip was scanned after a median of 80 (IQR 60-101) days. The DXA-scanner was a Hologic Discovery and NHANES III was used as reference material [26]. Low BMD level using total hip and neck BMD was defined as a T-score ≤ -2.5 [27].

X-rays

All x-rays were evaluated prior to the statistical analysis by the first author for fracture displacement, implant positioning and quality of reduction. Fracture displacement was assessed using the simplified non-displaced vs. displaced version of the Garden criteria [28, 29] due to low reliability of the four-grade system [30]. The implant positioning was assessed according to a modified version of Schep et al [10] (fig. 2a and 2b).

A point was given if:

a. The positions of the screws were within the central or caudal segment of the femoral head on the anterior-posterior view (fig. 2a)
b. The distance between the tip of the screws the articular margin of the femoral head were less than 10 mm (fig. 2a and 2b)
c. The positioning of the lowest screw was directly over the calcar in anterio-posterior view (fig. 2a)
d. The angle of the screws and the femur was more than 130 degrees (fig. 2a)
e. The positions of the screws were within the central or dorsal part on the axial view (fig. 2b)

A score of 4 points (maximum 5) was considered as adequate implant positioning. For the analysis the variable is therefore dichotomous with adequate or inadequate implant positioning.

A modified Garden's alignment index [31] was used to assess the quality of reduction (fig. 3a and 3b). On the AP view the central axis of the medial group of trabeculae in the capital fragment and the line of the medial femoral cortex was used to measure an angle (fig. 3a). On the axial view the anterior or posterior angulation of the head was measured by the angle between a line drawn from the midpoint of the fracture surface of the distal fragment to the centre of the femoral head and a line through the central axis of the neck of the femur (fig. 3b). In order for the reduction to be acceptable the anterior-posterior angle should be between 150-189 degrees and the axial angle less than 20 degrees. In Frandsen et al [31] they used two axial angle cutpoints (15 and 25 degrees) and here only one cutpoint is used due to work of Palm et al [32]. For the analysis the variable is therefore dichotomous with adequate or inadequate fracture reduction.

Failure predictors

Besides implant positioning and quality of reduction, age and gender were also recorded. Age was used as a dichotomous variable divided at 70 years. Two possible failure predictors were chosen from the questionnaire: For co-morbidity alcohol was chosen as the best variable because Duckworth et al [33] showed that it is an important risk factor for fixation failure for patients below 60 years. Excessive alcohol consumption was here defined as above 21 units per week for male and above 14 units per week for female. For patient function walking disability was chosen as a measurement of level of activities of daily living because it is a risk factor for not returning to home [34]. Walking disability was a yes/no question of the patients own evaluation of their walking abilities.

Primary covariate was BMD compared to failure of IF from date of surgery to date of extraction from The National Registry of Patients (November 9th 2010), reoperation or death (whatever came first). Secondary covariates were possible predictors of failure: displacement of fracture, implant positioning, quality of reduction, age, gender, co-morbidity and walking disability.

Statistical analysis

From the questionnaire twenty variables were chosen for investigation but only two variables (co-morbidity and walking disability) were included in the analysis in order to minimize mass significance and due to missing in the other variables. The statistical software program STATA 11 was used for the analysis. Data was set as survival data (observation until earliest of failure, death or end of study) and group comparison with log rank tests and Kaplan-Meier graphs showed heavy dependency of displacement. In order assess a potentially minor influence of the variables the Cox regression was stratified on fracture displacement. The proportional hazard assumption was evaluated statistically (goodness of fit) and graphically using log(-log) Kaplan-Meier survival plot against survival time. One variable (implant positioning) did not satisfy the proportional hazard assumption and was used as a time-dependent variable (multiplied by the logarithm of analysis of analysis time) as described by Kleinbaum and Klein [35]. The extended (time-dependent implant positioning) stratified (fracture displacement) Cox regression model was also adjusted for age, gender, quality of reduction, alcohol and walking disability.

Results

The failure rate for fracture displacement was 22 % (95 % CI 12;39) for the undisplaced fracture and 66 % (95 % CI 56;76) for the displaced fracture after two years. The overall failure by fracture displacement and total hip BMD level showed no difference of having low BMD or not (Fig. 4). The median time from operation to DXA scan was 80 days (IQR 60-101) and the median time to failure was 158 days (IQR 79-425). The median time from the DXA scan to failure was 86 days (IQR 4-280).

The preliminary log rank tests stratified for fracture displacement showed statistical significance only for implant positioning. The extended Cox regression was stratified on fracture displacement (therefore no results shown for fracture displacement) showed the same result with no association of low hip BMD and failure (table 2). There were no association between any covariate and failure besides implant positioning (HR 65.8, CI 3.5;1240, $p<0.005$). The analysis was also done with femoral neck BMD instead of total hip BMD and gave the same result (HR 1.11, CI 0.65;1.88, $p=0.711$). A subgroup analysis of the undisplaced fractures revealed no statistical significance of low BMD and failure (HR 6.22, CI 0.53;73.4, $p=0.147$) (table 3).

Discussion

The present study showed no association between low hip BMD and fixation failure. As in previous studies the most important predictor of failure was fracture displacement with 22 % failure in the undisplaced fracture and 66 % in the displaced [3]. In addition, implant positioning showed statistical significance ($p<0.005$) having a hazard ratio of 66. The lack of effect of the known predictors of fixation failure is probably a power issue because Parker et al [5] showed that a large sample size is needed to see the gender effect on fixation failure.

To our knowledge only 3 other clinical studies have investigated the effect of BMD on failure of internal fixed femoral neck fractures. Karlsson et al [36] investigated the changes of BMD in 47 femoral neck fractures and as secondary outcome they found no association of late segmental collapse or pseudoarthrosis and BMD. No information was given on displacement, implant positioning or quality of reduction. Heetveld et al [37] DXA-scanned all displaced femoral neck fracture patients and found no difference in BMD in patients with fixation failure compared to the group without failure. They had information on age, gender, implant positioning and quality of reduction but did not adjust for it in their analysis. The only study with all known potential confounders in their analysis is Spangler et al [38]. They found that patient with a registered ICD-9-CM code for osteoporosis in their files had a hazard ratio of 7.8 for revision surgery. Their register is most likely underestimating the prevalence of osteoporosis in their patients (9 %) because other studies have shown osteoporosis percentages as high as 88 % in this patient group [39, 40]. There is also a potential measuring bias because the osteoporosis diagnoses could come from low spine BMD.

Heetveld et al [37] had pre-operative BMD measurements and the present study had BMD measurements performed 80 days (IQR 60-101) after surgery. It is difficult to conclude what is best because neither study has an exact link between failure and BMD measurement and the present study had a median time from the DXA scan to failure of 86 days (IQR 4-280). Karlsson et al [36] had DXA-scan immediately after the fracture, 4 months and 12 months but did not have information of other failure predictors factors. When evaluating the results in the literature and the present study, factors that influences the hip BMD measurement must be taken into account. BMD of the hip is not constant and declines with 0.5-1.6 % per year in the elderly population [41, 42]. In patients with a hip fracture the decline one year after the fracture is greater and hip BMD ranges from 2-5 % [36, 43-46]. Such a decline in hip BMD is also seen in patients with tibial fractures [47, 48] and Achilles rupture [49] and is therefore due to inactivity. Other factors such as exercising and bone preserving drugs can also alter the decline of hip BMD [45, 50-53]. There is also a difference between a patient hips in hip BMD and it has been estimated to range from 6 % for total hip BMD [54] and to exceed the least significant change in 47-54 % for total hip BMD [55-57]. In hip fracture patients only one study have investigated the difference in BMD between the injured and uninjured side

[36] and for femoral neck fracture patients there was a difference of 20-29 % after 4 months and 1-6 % after 12 months. However, the reliability of the measurements must be questioned because the measured regions are very small and results have very high standard deviations. A study measured the difference after removal of an intramedullary nail and the difference was only 6 % for trochanter BMD [58]. Even though there might be a difference between the injured and uninjured hip it is probably not as large as measured by Karlsson et al [36].

There are limitations to this study. The association between osteoporosis and fixation failure might be small and our study therefore probably have a lack of power. Secondly, there is a selection bias since patients with severe co-morbidity and dementia are excluded and the mean time to the DXA-scan is 80 days. The 30-day mortality is therefore 0 % in this cohort and 6 % after one year. At the same time it is also a strength because we have very few censored data due to death. Lastly, there might be a measuring bias of implant positioning and quality of reduction since both measures have been modified slightly.
There are also strengths to this study. This is a population based study with a well defined cohort and external validity can easily be assessed. Secondly, low bone quality was measured with a DXA-scanner - the golden standard. Thirdly, the department had a strict guideline using IF for all femoral neck fractures and only seven patients received a different treatment. Finally, extracting data from The National Registry of Patients allowed us to find two additional patients with failure which normally would not be possible.

In a perspective view bone quality might be factor in IF failure. Although not significant, the subgroup analysis for the undisplaced fracture (table 3) shows a hazard ratio of 6.2 for low BMD compared to 0.8 in the main analysis (table 2). As mentioned in the introduction fracture healing is determined by three ideal conditions: adequate blood supply, good contact between bone fragments and good stability [16]. For the undisplaced femoral neck fracture there should be a normal blood supply and bone contact between the bone fragments and compared to the displaced fracture the major reason for failure might lay in the stability. Osteoporosis seem to affect the anchorage of screws [19-21] and therefore be a reason for lower stability in the undisplaced fracture and hence failure.

In conclusion we find that low hip BMD is not associated with fixation failure in femoral neck fracture patients treated with IF.

Conflict of Interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article

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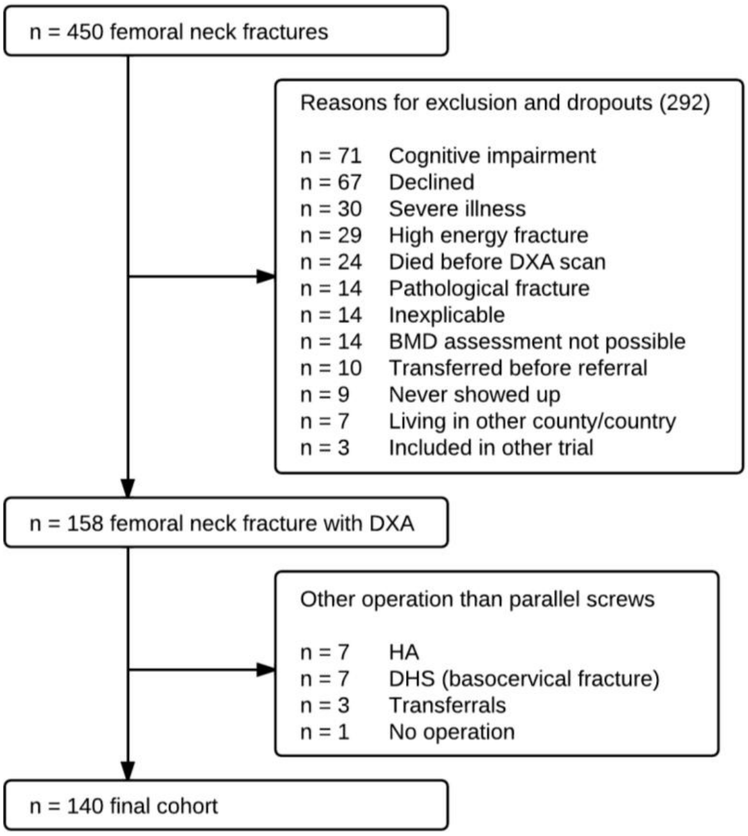
Figures

Fig. 1 Flowchart of patient enrolment



DXA: Dual-energy x-ray absorptiometry. BMD: bone mineral density. HA: hemiarthroplasty. DHS: dynamic hip screw.

Fig 2a Implant positioning assessment – anterior-posterior view

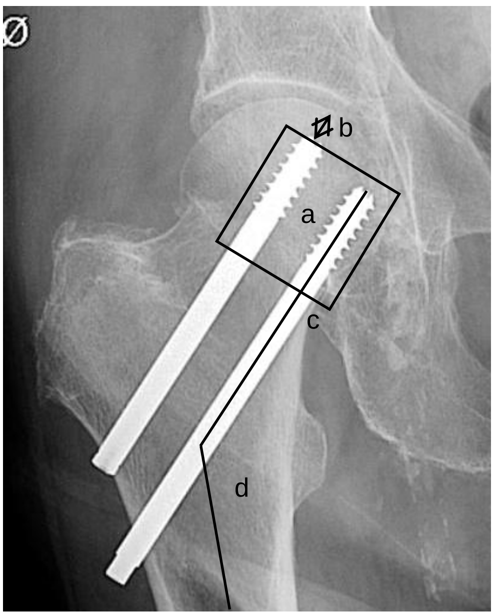


Fig 2b Implant positioning assessment – axial view

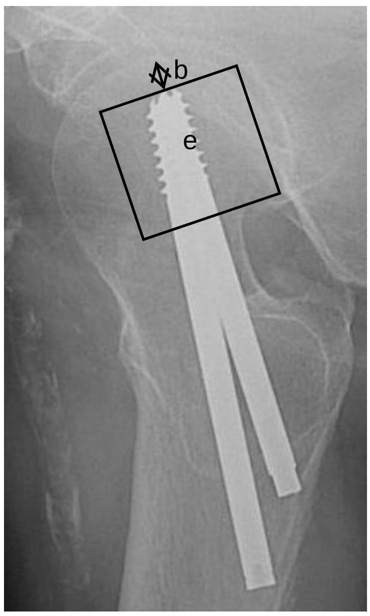


Fig. 3a Modified Garden's alignment index – anterior-posterior view

Fig. 3b Modified Garden's alignment index – axial view

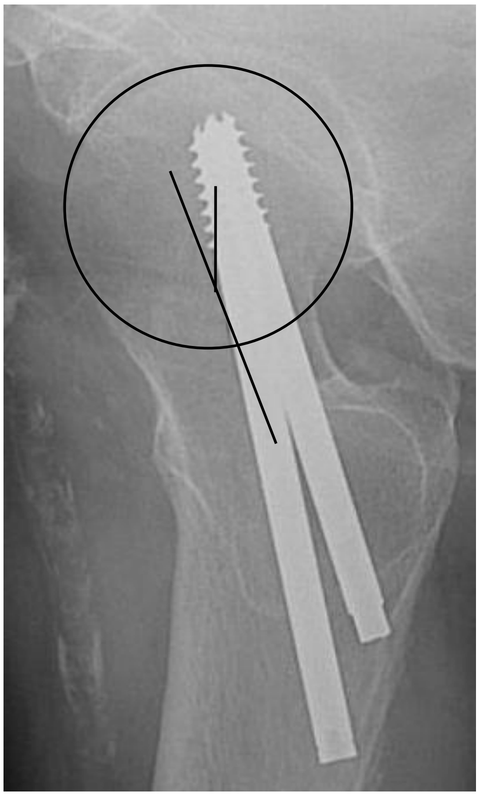
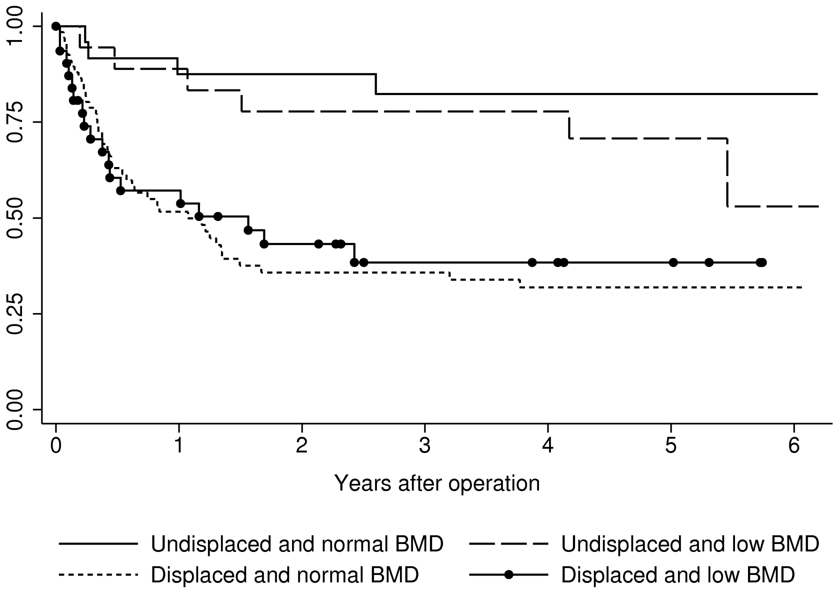


Fig. 4 Kaplan-Meier hip survival by fracture displacement and total hip BMD level



Tables

Table 1 Key patient demographics for 140 patients

	No failure	Failure	Total
Patients	70	70	140
Age (Inter Quartile Range)	82.1 (73.0-85.6)	78.7 (70.1-84.2)	80.1 (70.3; 84.9)
Gender	M21, F49	M14, F56	M35, F105
Undisplaced fracture	32	10	42
Displaced fracture	38	60	98
Total hip T-score > - 2.5	45	46	91
Total hip T-score ≤ - 2.5	25	24	49

Table 2 Results from the extended stratified Cox regression

	Hazard Ratio	95 % CI	p value
Low total hip BMD	0.82	0.46;1.47	0.506
Implant positioning	65.8	3.5;1240	0.005
Quality of reduction	0.76	0.38;1.49	0.423
Gender	1.49	0.76;2.93	0.249
Age	1.62	0.79;3.30	0.188
Alcohol	1.55	0.57;4.26	0.392
Walking disability	1.02	0.60;1.76	0.930

n=115 due to missing in one or more covariates

Table 3 Results from a subgroup cox regression of the undisplaced fractures

	Hazard Ratio	95 % CI	p value
Low total hip BMD	6.22	0.53;73.4	0.147
Implant positioning	21.9	1.64;292	0.020
Gender	5.90	0.31;112	0.237
Age	0.34	0.05;2.43	0.284
Alcohol	0.46	0.06;3.75	0.468
Walking disability	0.11	0.01;1.00	0.050

n=37 due to missing in one or more covariates

Paper 3

Reduced reoperation rate of cemented versus uncemented hemiarthroplasty and internal fixation of femoral neck fracture: 12 - 19 years follow-up of 75+ year old patients

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Søren Overgaard: Conception and design, revising article critically.

Jens Lauritsen: Conception and design, analysis and interpretation, revising article critically.

Ole Ovesen: Conception and design, revising article critically.

Abstract

Background and purpose: Elderly patients with displaced femoral neck fractures are commonly treated with a hemiarthroplasty (HA), but little is known about the long-term failure of this treatment. This study compared reoperation rates for 75+ year old patients with displaced femoral neck fractures treated with either internal fixation (IF), cemented HA, or uncemented HA (with and without hydroxy-apatite coating) with 12 to 19 years follow-up.

Methods: 4 hospitals with clearly defined guidelines for treatment of 75+ year old patients with a displaced femoral neck fracture were included. Cohort 1 (1991-1993): n=180, IF; cohort 2 (1991-1995): n=203, uncemented bipolar Ultima HA (Austin-Moore stem); cohort 3 (1991-1995): n=209, cemented Charnley-Hastings HA; cohort 4 (1991-1998): n=158, uncemented hydroxy-apatite coated Furlong HA. Data were retrieved from patient files, the region-based patient administrative system, and The National Registry of Patients at the end of 2010. Survival analysis was performed with adjustment for comorbidity, age, and sex.

Results: Cemented HA had a reoperation rate (RR) of 5 % and was set as reference in the Cox regression analysis which showed significantly higher hazard ratios (HR) for IF (HR 3.8 (95 % CI 1.9;7.48), RR 18 %) compared to uncemented HA (HR 2.2 (95 % CI 1.1;4.5), RR 11 %), and uncemented hydroxy-apatite coated HA (HR 3.6 (95 % CI 1.8;7.4), RR 16 %).

Interpretation: Cemented HA has a superior long-term hip survival rate compared to IF and uncemented HA (with and without hydroxy-apatite coating) for 75+ year old patients with displaced femoral neck fractures.

Introduction

The strategy for the treatment of the displaced femoral neck fracture has been discussed for years [1-3], and the issue is becoming increasingly important in the light of the growing number of elderly people with hip fractures as a consequence of an increasing life expectancy [4-6]. Internal fixation (IF) is associated with less initial surgical trauma, less blood loss and shorter operating time [7-9] but with a high reoperation rate varying from 10-57 % [10].

Primary arthroplasty has in short term studies been shown to have a much lower percentage of reoperations (4-32 %) [10], and cemented prostheses have been shown to have reduced post-operative pain and better mobility compared to uncemented prostheses [11]. 2 recent meta-analyses showed the same results but emphasized that the observations applied to older uncemented hemiarthroplasty (HA) designs [12, 13]. 2 randomized controlled trials (RCT) [14, 15] compared a cemented HA to an uncemented hydroxy-apatite coated HA. Both RCTs demonstrated good results for both HAs with no difference in complications, mortality or functional outcome after 1 year.

Most RCTs performed had a maximum follow-up time of 2 years, and hence little knowledge exists on the long-term performance of both IF and HA. 3 RCTs had a follow-up time above 10 years [16-18] and none of them included a hydroxy-apatite coated. Due to an increasing life expectancy, knowledge about the quality and the long-term results of the treatment of femoral neck fractures is becoming very important [19, 20]. Therefore, more studies of the long-term outcome of this treatment are needed.

The aim of this study was to compare reoperation rates for 75+ year old patients with displaced femoral neck fractures treated with either IF, cemented HA, or uncemented HA (with and without hydroxy-apatite coating) with 12 to 19 years follow-up.

Patients and methods

Patients

4 different hospitals with clearly defined guidelines for treatment of 75+ year old patients with a displaced femoral neck fracture were sought: 8 hospitals using different implants were identified and 3 had the following clearly defined guidelines: IF should be used for the undisplaced fracture and HA for the displaced fracture in patients aged 75+ years. A 4th hospital which used IF for all femoral neck fractures was also included. Thus 4 historically matching cohorts were identified at Odense University Hospital, Svendborg Hospital, Aarhus Municipal Hospital, and Hilleroed Hospital. The hospitals were anonymized and referred to as cohorts 1-4. All patients were primarily operated or supervised by a senior registrar. The same surgical procedure (postero-lateral) was used in cohorts 2-4 (HA). In these 3 cohorts patients with IF operations were excluded. The main part of these patients probably had an undisplaced fracture, but since all radiographs were destroyed, it was not possible to confirm how many fractures were displaced (Figure 1). Postoperatively, full weight bearing exercises from day 1 had been encouraged and similar drugs for thrombosis prophylaxis and antibiotics had been given. The patients had had up to 1 year regular follow-up after their operation.

<u>Cohort 1</u>

The first cohort included patients from a previous prospective, randomized study comparing IF and a dynamic hip screw [21]. Exclusion criteria were pathological fracture and patient not able/willing to sign an informed consent. During 01.03.1991 – 01.06.1993 260 femoral neck fracture patients were treated at the hospital. 80 patients were excluded from the study, mainly due to an undisplaced fracture (63), and 180 patients were included. No difference in reoperation rate was seen after 17 years of follow-up.

<u>Cohort 2</u>

During 1991 – 1995, hospital 2 used an uncemented bipolar Ultima HA which consisted of a one-size Austin-Moore stem, 190 mm long, 135 degree neck angle with a collar and a bipolar 42-56 mm Ultima head. There were 377 femoral neck fracture patients in that period, and 156 of those were excluded due to IF operations. 203 patients were included.

<u>Cohort 3</u>

During 1991-1995 hospital 3 used a cemented bipolar Charnley-Hastings HA. The Charnley stem was a one-sized flanged 40, 112.4 mm long, 130 degree neck angle, and a bipolar 36-56 mm Hastings head was applied. There were 362 femoral neck fracture patients in that period and IF was used in 148 patients. 209 patients were included.

<u>Cohort 4</u>

During 1991 – 1998 hospital 4 used a bipolar uncemented hydroxy-apatite coated Furlong HA. The Furlong stem was fully coated with hydroxy-apatite, in sizes 9-16 mm, 127 degree neck angle, and had a collar. The bipolar head came in sizes of 40-58 mm. There were 380 femoral neck fracture patients in that period and IF was performed in 189 patients and 223 patients were excluded. 157 patients were included.

Thus, 749 patients from the 4 hospitals were included in the present study (Figure 1). The number of patients at risk was 471 after 2 years, 375 after 5 years, and 199 after 10 years (Table 1).

Data

Patients were identified through procedure books and the region-based patient administrative system, and information on operation (date, side, type), reoperation (date, side, type), and date of death was recorded. In Denmark all residents have a unique personal identity number from The Civil Registration System, which contains data on vital status and residence for the entire Danish population [22]. The identity number enabled us to retrieve data on all patients from The National Registry of Patients (NRP), which was done on November 9th 2010. NRP was established in 1977 and contains data on all admissions and discharges from hospitals in Denmark, including dates of admission and discharge, surgical procedures performed, and up to 20 diagnoses for every discharge. The coding from the NRP has a consistently high positive predictive value [23] and was used to create a Charlson comorbidity index [24] with diagnosis codes up to 10 years before the patients' date of operation. The NRP also contained information about the reoperation data,, and all reoperations were confirmed in the patient files.

Failure was defined as any procedure that leads to major reoperation with loss/change of hip implant or periprosthetic/new fracture. A new fracture was defined as subtrochanteric at the level of IF implant or a femoral neck fracture more than 1 year after removal of IF. Reasons for failure were recorded as stated in the patient files or according to codes in the NRP. Patients were followed until first reoperation or until death, whichever came first. Minor procedures were defined as closed or open reduction (including change of bipolar head) and removal of IF. The codes for minor procedures were also extracted from the NRP, but as not all patients were admitted or coded correctly in that time period, there are some uncertainty about the completeness and accuracy of these codes, and therefore data on minor procedures were not included in this study.

Statistics

The statistical software program STATA 11 was used for the analysis. The term rate is used as proportion rather than outcome per time unit. A chi-square test for the categorical variables was used for group comparison before survival analysis. Data were set as survival data, and group comparison with log rank tests and Kaplan-Meier graphs were performed. The proportional hazard assumption was evaluated statistically (goodness of fit) and graphically using log(-log) Kaplan-Meier survival plot against survival time. A Cox regression analysis was applied with adjustment for comorbidity (Charlson index), sex and age. The Charlson comorbidity index score was categorized as done in the Danish Registry of Hip Fractures [25] (0, 1, 2, 3 or more points) and age was also categorized by 5-year intervals (75, 80, 85, 90 or more). To ascertain a possible theoretical influence of non-independence in patients with bilateral femoral neck fractures a sensitivity test was performed on the Cox regression analysis excluding the data on their second femoral neck fracture.

Results

The cohorts were similar with regard to age, sex, comorbidity, and survival (Table 2). Patients treated with a cemented HA (cohort 3) had the lowest overall reoperation rate of 5 % followed by uncemented HA and uncemented hydroxy-apatite coated HA (Table 2). For IF the number of reoperations was 33 (Table 2) and most of these were performed within the first 2 years after the primary operation (Table 1), leaving 82 % of the patients with their natural hip.

The cohorts had statistically (log rank test) significantly different reoperation rates (Figure 2). A chi-square analysis comparing the reoperation rates before and after 2 years (Table 1) shows no difference of IF compared to uncemented HA ($p<0.2$), but there were proportionally higher reoperation rates after 2 years for cemented HA ($p<0.001$) and uncemented hydroxy-apatite coated HA ($p<0.001$).

For IF, 28 of the 33 failures were osteosynthesis failure (Table 3). Periprosthetic fractures were the main reason for reoperations of HA with similar rates (13/22, 6/11, and 14/25 of the reoperations - Table 4).

The Cox regression analysis using IF as reference revealed a significantly reduced hazard ratio (HR) for cemented HA but not for uncemented HA or uncemented hydroxy-apatite coated HA (Table 5). In the Cox regression analysis that followed, cemented HA was used as reference in order to evaluate whether cemented HA had a different HR compared to the other HA. The analysis showed significantly higher HR for IF, uncemented HA, and uncemented hydroxy-apatite coated HA compared to cemented HA. The analyses were adjusted for comorbidity, age, and sex (all non-significant). A sensitivity test excluding the patients second fracture (n=25) showed only minor changes in HR’s, confidence interval’s, and p-values.

Discussion

We found a lower reoperation rate (18%) after IF at 19 years than has been found in meta-analyses, which found reoperation rates of 36 % [7-9], and compared to other long-term outcome studies of IF [16-18], which found reoperation rates of 33 – 46 %. Our finding might be explained by the fact that hospital 1 was a large teaching hospital with approximately 500 hip fractures per year and almost exclusively used IF for all femoral neck fractures for at least a decade prior to the study period. All surgical procedures were also done or supervised by specialist. Furthermore Denmark has national low reoperation rates after displaced femoral neck fracture and the reoperation rate was 18 % in the latest report from the National Hip Registry [25]. Minor procedures such as closed or open reduction (including change of bipolar head) and removal of IF are not included in the present study and must be taking into account when comparing IF and HA results.

During the last 3 decades, a variety of different types and concepts of HA have been used. In the present study, 3 different concepts were used: a bipolar uncemented HA (Ultima/Austin-Moore), a bipolar cemented HA (Charnley-Hastings), and a bipolar uncemented hydroxy-apatite coated HA (Furlong). The reoperation rates in RCT studies are comparable for cemented and uncemented HA [11-13] even though the uncemented Austin-Moore stem in other study types have inferior outcome [26]. A large difference between the groups in the present study did not occur until after 3-4 years (Figure 2). A RCT with 13 years follow-up [17] reported a reoperation rate for the uncemented HA of 24 % compared to 11 % in the present study. However, one RCT with a follow-up of 9-15 years using an uncemented HA found a reoperation rate of only 7 % [16]. The difference in the reoperation rates between the study by Parker et al [16] and our study could be the result of the nationwide search for reoperations through the NRP done in our study. The older uncemented HAs are still widely used worldwide whereas the Ultima/Austin-Moore HA is almost phased out in the Scandinavian countries [27, 28].

One RCT comparing a cemented HA with an uncemented hydroxy-apatite coated HA found similar reoperation rates [14]. The study showed a reoperation rate after 1 year of 7 % in the uncemented group (6 % in the cemented group) which is comparable to the present study after 1 year (12/157 = 8 %). However, our study showed that half of the reoperations occured after 1 year and the final rate was 16 %. The high reoperation rate in the present study could be due to the Furlong stem. In comparison, the study by Chandran et al. [29] found a reoperation rate of only 8 % in 112 patients after a follow-up of 3-14 years. Livesley et al. [30] compared an uncemented HA (Austin-Moore) with an uncemented hydroxy-apatite coated HA (Furlong) and found no significant difference in outcome after 1 year. A newly published study from the Norwegian Hip Fracture Register [31] showed a 5-year survival of 97 % for the cemented HA which was statistically significantly different from the 91 % survival for all the uncemented HA (almost exclusively hydroxy-apatite coated HA). This tendency is confirmed in the present study.

There are limitations to this study. Firstly, there were some deviations from the guidelines for cohorts 2-4 as a small proportion of the displaced fractures were treated with IF, thus introducing a small selection bias. Secondly, 2 different IF implants were used in cohort 1, but this is not likely to affect our results; Bhandari et al. [32] showed no difference in reoperation rate between the 2 implants. Thirdly, due to the low number of patients at risk after 10 years follow-up, the results hereafter are only considered to be indicative.

The strengths of the study are, firstly, the long follow-up time. In spite of the fact that many patients with femoral neck fractures have comorbidities, the life expectancy of an average 75-year old female is 82 in DK [19] and UK [33] which reflects that life expectancy may be longer also for patients with a fracture [20]. Secondly, all reoperations were validated on a case level using 4 matching cohorts with comparable guidelines but different implant types. Thirdly, few patients were lost to follow-up and all reoperations were found using a linkage to the NRP, which also made it possible to adjust for comorbidity. Lastly, all HAs were bipolar and therefore there were no potential confounders from the unipolar HA.

In conclusion, the reoperation rate and the hazard ratio were lower for cemented HA than for IF, uncemented HA, and uncemented hydroxyapatite-coated HA in 75+ year old femoral neck fracture patients after up to 19 years follow-up, and our findings, therefore, suggest that cemented HA is the best treatment of a displaced femoral neck fracture in this patient group.

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No competing interests declared

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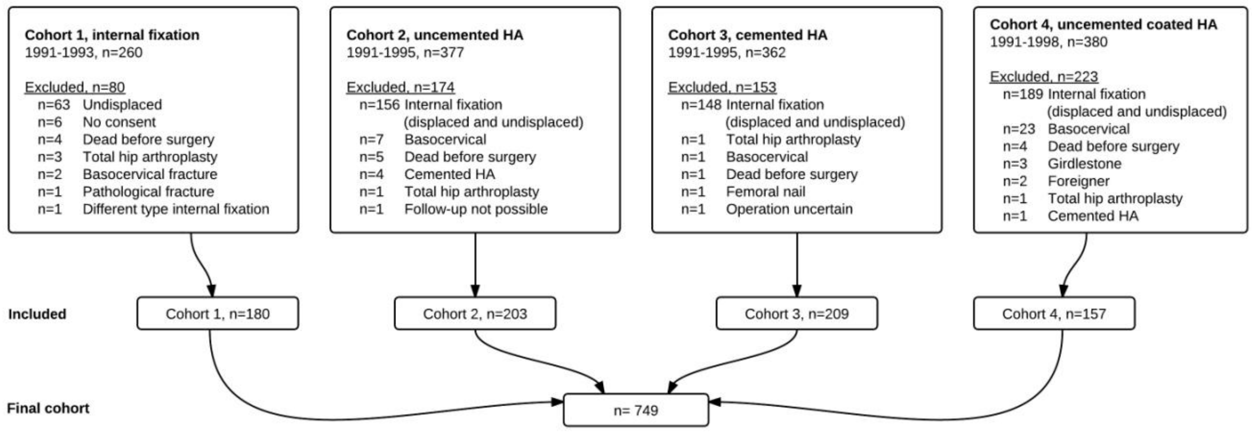
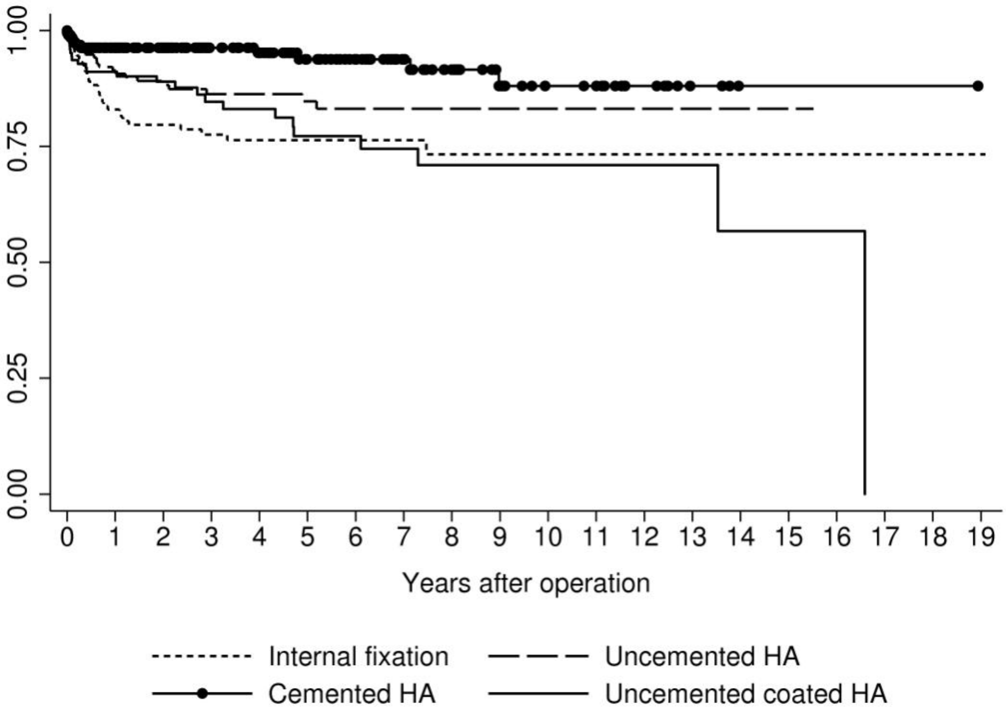
Figures

Fig. 1 Flowchart describing the cohorts with inclusions and exclusions



HA: hemiarthroplasty. Coated: hydroxy-apatite coated

Fig. 2 Kaplan-Meier implant survival curves by operation type



HA: hemiarthroplasty. Coated: hydroxy-apatite coated

Tables

Table 1 Reoperations by implant, for patient at risk attrition was mostly due to high mortality.

		Year 1	Year 2	Year 3-5	Year 6-10	Year 11-19
Internal fixation	Patients at risk	180	105	82	41	13
	Number of reoperations	25	4	3	1	0
Uncemented HA	Patients at risk	203	125	99	54	15
	Number of reoperations	14	4	3	1	0
Cemented HA	Patients at risk	209	147	120	65	19
	Number of reoperations	7	0	2	2	0
Uncem coated HA	Patients at risk	157	94	74	39	9
	Number of reoperations	12	2	7	2	2
Total	Patients at risk	749	471	375	199	56
	Number of reoperations	58	10	15	6	2

HA: hemiarthroplasty. Uncem coated: uncemented hydroxy-apatite coated

Table 2 Key patient demographics for 749 patients in the 4 cohorts

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	p-value
Number of patients	180	203	209	157	-
Type of operation	Internal fixation	Uncemented HA	Cemented HA	Uncem coated HA	-
Median age (IQR)	83 (79–87)	84 (80–87)	83 (79–88)	85 (80–89)	0.2
Sex (female/male)	129/51	163/40	169/40	127/30	0.09
Median CCI score (IQR)	2 (0-3)	1 (0-3)	1 (0-3)	1 (0-3)	0.4
Median pt survival, years (IQR)	2.8 (0.1-9.9)	2.5 (0.1-9.7)	2.9 (0.1-10.7)	2.2 (0.0-9.0)	0.5
Failure (%)	33 (18.3)	22 (10.8)	11 (5.3)	25 (15.9)	See table 5

HA: hemiarthroplasty. Uncem coated: uncemented hydroxy-apatite coated. IQR: inter quartile range. Pt: patient CCI: Charlson comorbidity index.

Table 3 Reasons for reoperation

	Internal fixation	Uncemented HA	Cemented HA	Uncem coated HA
Osteosynthesis failure	28	0	0	0
Arthrosis	4	2	0	0
Dislocation	0	3	5	8
Loosening	0	2	0	0
Periprosthetic fracture	0	13	6	14
Infection	1	2	0	2
Unknown	0	0	0	1
Total	33	22	11	25

HA: hemiarthroplasty. Uncem coated: uncemented hydroxy-apatite coated

Table 4 Type of reoperation

	Internal fixation	Uncemented HA	Cemented HA	Uncem coated HA
THA	24	8	5	13
Cemented HA	6	3	0	3
Girdlestone	2	1	0	1
Osteosynthesis	0	10	6	8
Reosteosynthesis	1	0	0	0
Total	33	22	11	25

HA: hemiarthroplasty. Uncem coated: uncemented hydroxy-apatite coated. THA: total hip arthroplasty

Table 5 Survival analysis of hip failure adjusted for sex, co-morbidity and age (all non-significant)

	HR	95 % CI	p-value	HR	95 % CI	p-value
Internal fixation	1 (ref)			3.8	1.9 – 7.5	< 0.001
Uncemented HA	0.6	0.3 – 1.0	0.05	2.2	1.1 - 4.5	0.035
Cemented HA	0.3	0.1 – 0.5	< 0.001	1 (ref)		
Uncem coated HA	1.0	0.6 – 1.6	0.9	3.6	1.8 – 7.4	< 0.001

HA: hemiarthroplasty. Uncem coated: uncemented hydroxy-apatite coated. HR: hazard ratio. CI: confidence interval.