Hip fracture epidemiology and treatment

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*Series of dissertations submitted to the
Faculty of Medicine, University of Oslo*

ISBN 978-82-8333-282-7

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Cover: Hanne Baadsgaard Utigard.
Print production: Reprosentralen, University of Oslo.

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Acknowledgements

I would like to express my sincere gratitude to my three supervisors, their qualities complement each other. Cathrine M. Lofthus has been a thorough main supervisor. She has contributed invaluable knowledge on all formal processes together with continuous supervision on all aspects of this thesis and scientific work. In addition, I have enjoyed the time we have had together.

Lars Nordsletten sees opportunities where others do not. He has also shown great enthusiasm throughout the project, and he arranged for me to be a part of the staff at Ullevål Hospital, for which I am truly grateful.

Frede Frihagen is a great friend and has been an invaluable supervisor. His clear and honest comments and his great knowledge have advanced my thinking every time we have discussed different subjects. Furthermore he initiated and conducted the randomized study on treatment of femoral fractures which I have followed up. I am grateful for his support and agreement to this. In this work, research coordinator Kenneth Nilsen was central in organising and controlling patient flow.

I would also like to thank my co-authors, especially Jan A. Falch who did the first hip fracture incidence study in Oslo in the late 1970s.

Being a doctoral student in the orthopaedic department has been an enjoyable experience, much thanks to my fellow PhD-students. A special thanks to Elisabeth Ellingsen Husebye, Berte Bøe and Ida Sletten for always being there, and to my colleagues at the arthroscopic surgery unit for being the reason why I always look forward to go to work.

I also want to thank Asbjørn Hjal for giving me a position at Ringerike Hospital that was important for my clinical career. I am grateful for his understanding, and for urging me to finish my thesis.

My parents have always valued academic knowledge. They have encouraged interest and curiosity in nature and in trying to understand how things are interrelated. They have always been supportive for me and my sisters. The values they taught me have been an important reason for me to pursue and complete a doctoral thesis.

My husband André is also my best friend. I am grateful for his continuous support and love. I also want to thank our daughters Aurora and Sunniva for being a continuous reminder of family as the most important thing in life.

Abbreviations

FCF Femoral neck fracture

FNF Femoral neck fracture

HA Hemiarthroplasty

IF Internal fixation

THR Total hip replacement

NPR National Patient Registry

NHFR Norwegian Hip Fracture Registry

CI Confidence Interval

SD Standard Deviation

ADL Activity of Daily Living

EQ-5D European Quality of Life-5 Dimensions

HHS Harris Hip Score

BI Barthel Index

NOMESCO Classification of surgical procedures by The Nordic Medico-Statistical Committee

ICD-10 International classification of Diseases – 10th revision

RCT Randomised controlled trial

PROM Patient reported outcome measure

FDA U.S. Food and Drug Administration

DXA Dual-energy X-ray Absorptiometry

BMD Bone mineral Density

HRT Hormone Replacement therapy

List of papers

Paper I

Hip fracture incidence is decreasing in the high incidence area of Oslo, Norway;

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Osteoporos Int. 2012 Oct;23(10):2527-34. doi: 10.1007/s00198-011-1888-3. Epub 2012 Jan 14.

PMID:22246602

Paper II

Hospital databases are imprecise for epidemiological research;

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Submitted

Paper III

Hemiarthroplasty or Internal Fixation for Displaced Femoral Neck Fractures: A randomized study of six year follow-up;

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Clin Orthop Relat Res. 2014 Jan;472(1):360-7. doi: 10.1007/s11999-013-3245-7. Epub 2013 Aug 24.

PMID: 23975250

Summary

Introduction

Life changes after a hip fracture. Although much effort is spent to optimize treatment, still 25 % of the patients are deceased within a year, and more than half of the patients previously living independent, are institutionalized after a hip fracture. Hip fractures are common in the Norwegian population, with a total number of approximately 10 000 fractures per year [1]. The incidence is increasing exponentially with age [2]. Optimal treatment is important to improve outcome after a fracture, and preventive measures will save lives, pain and resources. The most common reason for hip fracture is osteoporosis and hip fracture incidence is thus a marker of osteoporosis. Development of hip fracture incidence over time can thus be the basis for hypothesis about risk factors and treatment for osteoporosis in a community.

Materials and Methods

Paper I and II were based on identification of hip fracture patients in Oslo, Norway in 2007. Electronic discharge registers and operation theatre protocols were used to identify patients, and charts were reviewed to verify the presence of a new hip fracture. Paper III studied treatment of patients with intracapsular hip fractures prospectively randomized to receive treatment with either internal fixation (IF) with two parallel screws or hemiarthroplasty (HA). The patients were examined after median 6 years using questionnaires to establish hip function (HHS), ADL function (Barthel Index) and Quality of Life (EQ-5D).

Results

A total number of 1,005 hip fractures in 985 patients were verified in Oslo, Norway in 2007. These fractures were regarded as the gold standard for hip fractures in Oslo in 2007, and the data registers were validated against this. Sensitivity of the hospital diagnosis registers, e.g. if the register contains all fractures, varied between 95 % and 99 %. Norwegian Patient Registry overestimated the number of fractures by 5 % when using the diagnose codes alone. Only 69 % of the fractures were registered in the Norwegian Hip Fracture Register compared with the gold standard. Sensitivity of this register

was 69 % in total, varying between 29 % and 89 % between the individual hospitals. The incidence of hip fractures in Oslo decreased significantly between 1996/97 and 2007. It was estimated that the use of bisphosphonates may explain up to 13% of the decline in incidence in women aged 60-69 years and up to 34 % in women aged 70-79 years.

Only 30 % of the patients in the randomized study were alive after 6 years and there were no difference between the two groups in mortality. No difference in hip function, ADL function or Quality of life was found. However, only 12 of 31 patients in the group of IF still had their native joint as a result of more than 60 % reoperations in the group.

Conclusion

The incidence of hip fractures in women in Oslo has decreased significantly during the last decade, and is now at a lower level than in 1978/79. Incidence data on hip fracture in Oslo, Norway, have been collected in a standardized way every decade since 1978/79 to reduce risk of wrong conclusion due to poor data register quality. Although hip fracture is a straightforward diagnosis, electronic diagnosis registers are inaccurate for this diagnosis. The unpredictable degree of both over- and underestimation makes it difficult to apply correction algorithms to improve data quality. Hence, when using data from registers additional processing and information are required to improve validity.

Hip fracture patients have high mortality. Hemiarthroplasty is the treatment of choice after femoral neck fractures compared with internal fixation due to superior short time results with comparable long term results.

Introduction

Hip fractures – definition and diagnosis

What is a hip fracture?

Hip fracture is a collective term on fractures in the upper thigh bone. The Latin name of the thigh bone, femur, will be used in the following. Hip fractures can be divided into fractures of the neck of femur and fractures in the trochanteric region [3]. Some publications also include sub trochanteric fractures [4]. They are, however, few in number in the elderly compared to the common femoral neck fractures and the trochanteric fractures [5]. Fractures in the femoral head are rare and most often a result of a dislocated hip joint [6]. They are not included in the term hip fracture. Common for all hip fractures is that the incidence increases exponentially with advancing age [7][8]. They are thus a marker on both fragility of bone and frailty of the patient.

The link between fracture risk and reduced bone mineral density is well established [9], but cannot explain an exponential increase in incidence. This indicates a complex interplay of risk factors including frailty of the patient as well as fragility of bone.

Figure 1. Different regions of hip fracture in proximal femur.

Femoral neck fractures are also termed intracapsular because they occur within the joint capsule.

The blood supply to the femoral head is completely dependent on arteries through and on the surface of the neck, and a fracture of the neck will often disrupt the blood supply to the entire head [10]. This result in healing problems of the fracture and frequent necrosis of the femoral head which requires special consideration in the surgical treatment and will often require a replacement arthroplasty.

The trochanteric fractures involve bone with good local blood supply. However, it occurs between the greater trochanter, where the gluteus medius and the gluteus minimus (hip extensors and abductors) attach, and the lesser trochanter, where the iliopsoas (hip flexor) attaches. These complex muscle insertions pull the parts of the fracture which may results in malunion if the internal fixation is unstable, or healing time is prolonged [11].

Diagnosis

Trauma to the hip followed by pain and inability to bear weight is indicative of a hip fracture in the elderly patient. If the patient can't raise the leg straight from the bed it is suggestive of a fracture. In demented patients, loss of function can be the only sign of a fracture. Plain radiographs in two planes are usually enough to verify the diagnosis with a sensitivity of 92-98 % [12]. In a Norwegian study from Ullevål University Hospital, only 2.5 % of the fractures were missed using conventional radiographs [13]. Occult fractures are, however, not uncommon due to the large number of hip fractures over all. Because of the high content of trabecular bone in the upper femur, disruptions can be more difficult to spot than in cortical bone. CT and scintigraphy have been used in evaluation of these patients. There is little data to support the use of CT, and several studies show a low sensitivity for detecting a fracture [14,15]. Scintigraphy has, in contradiction to CT, high sensitivity, but low specificity in this age group [16]. If the suspicion of a fracture still is high after negative radiographs, MRI is the preferred diagnostic tool because of relatively high sensitivity and specificity together with imaging of the extent of the fracture. This can be decisive for further treatment [12].

Consequences of a hip fracture

Hip fractures have important consequences both for individuals and society. For persons over 50 years, hip fracture is among the ten most incapacitating conditions worldwide in term of disability-adjusted life years [17]. One year mortality after a hip fracture is 20-27 % [18,19]. The hip fracture patients are elderly, and there is also a substantial one-year mortality among their peers. However, the one-year standardized mortality rate in the hip fracture population was around 3-4 times the expected for the age [20]. It is difficult to define how much of the excess mortality that is directly attributable to the fracture itself. Impaired health is often present before the fracture incident, and on average a hip fracture patient has three comorbidities [21]. The hip fracture may just as well be a marker for frailty as the cause of the excess mortality in itself. However, immobilisation, treatment and complications has negative impact on health, and can cause severe illness and mortality in addition to reduced quality of life [22]. Of the 80 % of hip fracture patients that walk independently before

the fracture, only half of them were able to do so after the incident [23]. Furthermore, half of the patients previously living independently remain in a long-term care or needed help with activity of daily living one year after the fracture [24]. At community level, hip fractures have a huge financial impact. It is estimated that the treatment of osteoporotic fractures in Norway costs society about 2 billion NOK annually [1]. Recent studies have indicated that orthogeriatric care for these patients can improve mobility and ability to manage activity of daily living and is likely to be cost-effective [25]. There is need to maintain a high standing treatment capacity and competence, as well as financial resources to improve care for hip fracture patients [19,26].

Hip fracture probability and risk factors

A hip fracture is a result of I) a trauma to the bone and II) a bone with a quality that cannot withstand the impact of the trauma

Trauma

In Norway 10 % of all hospital admissions are due to trauma [27]. The most common reasons for hospitalisation following a trauma are fractures, contusions, and joint dislocation/sprain. Trauma finds its roots in the Greek word for “a wound” or “damage” and can be defined as a physical injury caused by violent or disruptive action or by the introduction into the body of a toxic substance [28]. The result of trauma varies widely, from no or minor injury to lethal injury in the multitraumatized patients. Trauma patients are often categorized based on high or low energy injuries [29]. A hip fracture is usually the result of a low energy impact most often defined as a fall from standing height or lower [30]. This has led to fall preventive measurements both to reduce the susceptibility of falling and to reduce the impact of a fall.

Measurements aiming to reduce the impact of a fall include hip protectors. Hip protectors are either of the "crash helmet type" or "energy-absorbing type". The "crash helmet type" distributes impacts into the surrounding soft tissue, while the "energy-absorbing type" is made of a compressible

material and diminishes the force of impact. Both of these systems aim to reduce the focused force beneath an estimated fracture threshold. Hip protectors may prevent fracture when used, but adherence to use is low [31,32].

Susceptibility to fall is dependent on several risk factors that either increase risk of syncope/dizziness or alter a person's core balance. Environmental hazards such as slippery floors, loose carpets or electrical wires are obvious risk factors for falling. Icy roads have also been suggested as an explanation on the high incidence of hip fractures in Scandinavia. Studies have, however, not been able to demonstrate a seasonal variation in hip fracture incidence, maybe as a result of the majority of hip fractures occurring indoors [33]. Sedative use, cognitive impairment, and disability of the lower extremities are shown to be of greatest importance regarding susceptibility of fall [34]. Persons on medication are shown to have an increased fall risk [35]. This is especially true for users of cardiac medication that lowers blood pressure (anti-arrhythmic, non-selective beta blockers) and increases risk of syncope. In a meta-analysis, Leipzig and co-authors found that digoxin, type IA antiarrhythmic, and diuretic use were weakly associated with falls in older adults. No association was found for the other classes of cardiac or analgesic drugs examined. Persons taking three or more medications had an increased risk of falling [36].

Also patients taking medications that can cause dizziness (benzodiazepine, anticonvulsants, and antidepressants) , are of increased risk of falling [37]. Care should be taken before prescribing these drugs to elderly. These studies are, however, observational studies and confounders are likely to be present. No studies have examined if discontinuing medication will reduce risk of falling.

In a study on falls in elderly people residing in long-term care, the researchers found that incorrect weight shifting was the most frequent cause of fall (41 %) [38]. Slipping accounted for only 3 % of falls. Centre-of-mass perturbations was a more frequent reason for fall than base-of-support perturbations. Exercise programs with focus on balance reduce the risk of falling [39]. In persons with risk of falling; home safety interventions, vitamin D supplementation in people with lower vitamin D

levels, and individually targeted multifactorial interventions are associated with fewer falls [39]. This is also true for interventions for impaired vision. An umbrella review of meta-analyses showed that there is consistent evidence that exercise and individually tailored prevention reduces risk of fall in community-dwelling elderly [40]. The authors also found the same tendency in hospital based settings [41].

Bone quality and osteoporosis

The most important reason for fragile bone in the elderly is osteoporosis. Osteoporosis means “porous bone” and is characterized both by a decrease in bone mass and density, destruction of microarchitecture, and reduced protein content. The definition of osteoporosis by the World Health Organisation (WHO) is a bone mineral density (BMD) 2.5 or more SD below the average of a young healthy person of same sex and heritage, measured by dual x-ray absorptiometry (DXA).

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Figure 2. Structure of normal and osteoporotic bone, respectively

It is assumed that 240 000 persons in Norway have osteoporosis based on DXA-measurements [42].

Measurement site will influence this because the bone mass can differ from for example hip to

forearm. DXA is the most widely used way of estimating bone strength, both in a clinical setting and in research. DXA correlates with fracture risk [43,44]. DXA is an area measurement and it has been argued that it does not take into account the volumetric properties of the bone [45]. Therefore other ways of measuring bone content are used, especially for research. This include quantitative computer tomography (QCT), MR spectroscopy, and biopsies [46]. High cost, high radiation exposure and invasive technique limit their use in clinical practice.

Risk factors for osteoporosis

The dominating cause of osteoporosis is age [47]. During childhood, bones grow and repair quickly. Peak bone mass is reached on average during the third decade of life [48]. There is a delicate balance between osteoblasts that form new bone matrix and osteoclasts that remove old or damaged bone [49]. Many factors influence bone mass accumulation during growth including heredity, gender, dietary components (energy, proteins, calcium), mechanical forces and exposure to risk factors [50]. With aging, bone metabolism alters and bone loss occurs gradually. Until menopause, however, the bone mass remains almost unchanged in healthy individuals. The loss of oestrogen during menopause alters bone metabolism both by lack of inhibition of bone resorption and reduced deposition of bone [51,52]. This makes females more prone to develop osteoporosis than men.

Risk factors for developing osteoporosis can be divided into modifiable and non-modifiable. Non modifiable risk factors consist of age, sex (female), heredity [53], race [7], and small stature [54]. Small stature is, however, not clearly established whether it is a risk factor or a consequence of osteoporosis due to vertebral fractures [55]. Among the modifiable risk factors, nutritional deficiencies are important. Calcium metabolism plays a significant role in bone formation. The serum calcium level is closely controlled by two pathways; one is signaled to turn on when blood calcium levels drop below normal and one is the pathway that is signaled to turn on when blood calcium levels are elevated. Low serum levels leads to increased bone resorption. The body thus uses the skeleton as a calcium reservoir to maintain calcium homeostasis in other tissues. Lack of calcium and

Vitamin D also leads to impaired bone deposition [53], and Vitamin D impairment is an independent risk of hip fracture in an elderly population [56]. Underweight also affect bone health negatively. Even moderate underweight (BMI <22) is a risk factor for osteoporosis [57]. Endurance athletes, particularly females with amenorrhea, have decreasing femoral neck BMD when maintaining training, and a study found 6.5% bone loss in femoral neck during two years of heavy training [58]. On the other side of the motion spectrum, inactivity has similar effects on the skeleton. The regular loading of bone is an important stimulus for bone formation [59]. Dietary intake of heavy metal is also known to have a negative effect on bone health [60]. Smoking has a negative effect on bone health, but the mechanisms are unclear [61]. Alcohol consumption increases fracture risk, but if it has a direct effect on bone is not clear [62].

Medical illnesses known as risk factors for osteoporosis are hypo gonadal states with lack of oestrogen and testosterone, endocrine disorders e.g. Cushing's syndrome, renal disease, parathyroid disorders and thyroid gland disorder, and disorders associated with malabsorption such as coeliac disease, Crohn's disease and other inflammatory disorders [63,64]. It is not clear whether inflammatory diseases directly increase risk of osteoporosis or if the use of medication such as glucocorticoids is responsible.

Risk factors for osteoporosis

Nonmodifiable	Potentially modifiable
Advanced age[47]	Excess consumption of alcohol[62,65]
Female sex[33]	Vitamin D deficiency[53,66]
Estrogen deficiency[51,52]	Tobacco smoking[61,67]
Early menopause/hysterectomy[51,52]	Soft drinks[68]
Decrease in testosterone levels in men[69]	Malnutrition[70]
European or Asian race[7]	High dietary protein from animal sources[71]
Heredity[53]	Immobilization[59]
Small stature[54]	Underweight/inactive[70]
	Endurance training[58]
	Heavy metals[60]
	Endocrine disorders[63,64]
	Inflammatory diseases and corticosteroids[72]

Table 1. Common risk factors for osteoporosis.

Due to the multifactorial cause of fragility fractures, a better risk estimate for a fragility fracture than BMD alone has been advocated by the WHO [73]. The total individual 10-year fracture risk (AR-10) takes into account patients with high risk due to other risk factors of fragility fracture than just BMD. The AR-10 is calculated based on advanced age, prior fragility fracture, parental history of proximal

femur fracture, low BMI, low bone mass, glucocorticosteroid treatment, rheumatoid arthritis, smoking, and overuse of alcohol. FRAX® has been developed by the WHO and is a calculation tool for 10-year fracture risk [74]. The calculation tool takes into account the different incidence of hip fracture in the different countries and is country specific [75]. There is no general agreement on treatment recommendations based on FRAX. In some countries guidelines are provided based on expert opinion and/or health economics [76].

Treatment of osteoporosis

The main consequence of osteoporosis is increased fracture risk and any treatment should be aimed at reducing this risk. Modifiable risk factors for osteoporosis should be treated. Supplementation of vitamin D and calcium, prevention of malnutrition and underweight, smoking cessation and the treatment of medical disorders are examples of risk reduction strategies. Targeted medical treatment is dominated by the use of bisphosphonates. Bisphosphonates work by inhibiting the osteoclasts responsible for bone resorption [77]. Bisphosphonates were introduced on the Norwegian market in 1996. Taken orally or intravenously they reduce the risk of hip fractures with approximately 40 % and clinically diagnosed vertebral fractures with 55 % [78,79]. In June 2010 a new anti-resorptive drug was approved by the FDA. Denosumab is a monoclonal human antibody with high affinity and specificity for rank ligand (RANKL) and inhibits its action. RANKL is a nuclear factor-kappa- β ligand that is essential for osteoclast differentiation, activation, and survival [80]. Denosumab has proved at least as efficacious as bisphosphonates [81]. Ease of administration (subcutaneous injection every 6 months) makes it a good alternative to bisphosphonates. Anabolic agents for treatment of osteoporosis consist of hormone replacement treatment (HRT) and synthetic parathyroid hormone (PTH), teriparatide. Teriparatide was used by less than 100 persons in Norway before 2007 [82].

HRT is used to supplement oestrogen loss. Loss of oestrogen with menopause causes accelerated bone loss. Oestrogen induces apoptosis in osteoclasts and prevents apoptosis in osteoblasts [83]. It also reduces fracture risk and increases BMD according to clinical studies. However, serious side

effects such as of increased risk of cardiovascular disease and breast cancer [84,85] have led to an almost complete stop in the use of HRT as treatment for osteoporosis [86]. HRT is, however, still used for other indications such as post-menopausal complaints and could thereby affect the fracture incidence.

Epidemiology

Incidence

Incidence means the number of new incidents per population per time unit. In hip fracture research it is usually reported as new fractures per 10 000 inhabitants per year in a defined geographical area. The hip fracture incidence increases exponentially with age [33]. Lofthus also demonstrated that Oslo had the highest hip fracture incidence ever published until 2001 [33]. A variety of studies have examined hip fracture incidence in different regions of the world. There is a 10 fold range in hip fracture incidence worldwide [87]. The Nordic countries have very high incidence of hip fractures while African countries have among the lowest incidence. North America, Russia, Oceania and Southern America are in a moderate risk group. Osteoporosis is more common in the cities than in rural districts [88,89].

The age standardized incidence of hip fracture is approximately two times higher in women than in men [33]. In Norway one could expect a seasonal variations in hip fracture incidence because of long, cold winters with slippery roads, but this has not been demonstrated [33]. For forearm fractures, seasonal variations are, however, present [90]. The reason why hip fracture incidence is not affected by weather is probably because most fractures occur indoors and is a result of falling from standing height [30].

As hip fracture incidence increases with age, adjustments to a standard population have to be done in order to compare different geographical regions. This is done by applying age specific rates to the standard population chosen [91].

Trends in hip fracture incidence

Towards the end of the millennium, the number of hip fractures in several parts of the world increased more than can be accounted for by demographic changes alone [2,33,92,93]. It was projected that the annual number of hip fractures would increase more than tenfold during the next 50 years [2]. However, reports from the Nordic countries during 1990s indicated that there was a trend brake and the incidence was no longer increasing [33,94-96].

Data source

Electronic data registers are readily available sources for large amounts of data. However, the quality of data in the register is essential for its usefulness. Different sources of error will vary in frequency between different registers. Over- or under reporting will be common in some registers because of administrative errors, whereas other registers will have a skewed entry where for example the more serious cases are over- or underreported [97]. Registers linked to financial reimbursement will perhaps be prone to over-reporting due to misleading diagnosis codes, and clinical registers may be vulnerable to under-reporting [98].

Classification systems

NOMESCO

Nordic Medico-Statistical Committee (NOMESCO) is a statistical committee under the Nordic Council of Ministers and was set up in 1966.

At the initiative of NOMESCO a common Nordic classification for surgical procedures (NCSP) was presented and approved at a Nordic seminar in November 1991 [99]. The NCSP is kept updated by national committees, in Norway this is the responsibility of The Norwegian Directorate of Health [100].

ICD-10

ICD is an abbreviation of International Classification of Diseases, a short form of International Statistical Classification of Diseases and Related Health Problems. The list was made by the WHO for statistical purposes. It contains codes for diseases, signs and symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or diseases [101]. ICD is also used for reimbursement and resource allocation decision-making by countries, and national clinical modifications have been made. The Norwegian Directorate of health is responsible for updates in Norway. ICD-10 is the tenth revision and came into use in WHO Member States as from 1994.

Hospital databases

Before computers were introduced in the hospitals, data lists were handwritten or written on a typewriter. In hospitals, a wide range of lists have been maintained, for example admission lists, discharge lists, operation theatre protocols, and register of radiographs taken. Handwritten operation theatre lists are still used in some hospitals. However, electronic lists of key information are found in all Norwegian hospitals. Discharge registers are one of these. On discharge, the physician writing the report is responsible for entering the relevant diagnoses from the hospital stay, either directly into the database or by notifying a secretary. In some hospitals, a staff member will check the diagnoses later.

Norwegian Patient Registry (NPR)

NPR is operated by The Norwegian Directorate of Health, a subordinate agency to the Norwegian Ministry of Health and Care Services. When a patient is referred to a hospital or specialist, many variables are stored in databases. A selection of information is transferred to NPR according to Norwegian regulations, including ICD-10 and NOMESCO codes. The purpose of NPR is to form the basis for administration, management, and securing quality of the health service. This also forms the basis for activity-based funding. Furthermore the register will contribute to research including

studies that can provide knowledge on healthcare, treatment effects, diagnosis and disease causes, prevalence and course of preventive measures as well as form the basis for quality registers.

Until 2008, the hospitals reported to NPR anonymously. One patient had only one entry to NPR each calendar year (per hospital) and was hence reported with the same code at consecutive stays within the same calendar year. If the patient was admitted to another hospital, he or she was reported with a new code to the register. From 2008, the register is coupled to the national identification number and the patients could be followed also between hospitals.

Quality registers

There are several local and national patient registers in Norway. The Norwegian Hip Fracture Register (NHFR) is located at the Norwegian Arthroplasty Register in Bergen, Norway, and started collecting information in January 2005 [102]. All hospitals in Norway with hip fracture surgery are encouraged to report every operation to the register. This is done by the operating surgeon. A hard copy form is filled out by hand and collected by a secretary and mailed to the register in Bergen. This requires informed consent from the patient. The manual routines of reporting are a source of register errors.

Use of epidemiologic data

Data registers have been of high importance for understanding diseases. The first national patient register in the world was established in Bergen, Norway in 1856. This was a register of patients with Leprosy[103,104]. The register was used by G. H. Armauer Hansen to establish that the incidence (new cases) of the disease was dependent of the prevalence (number of patients) 5 years earlier. He thereby argued that the disease was not hereditary as previously thought, but rather infectious. This altered how the disease was treated in terms of isolating patients in hospitals. Today, the health registries give useful figures and statistics that describe the historical situation and rises hypothesis about cause and effect. Registers are particularly useful for understanding common health problems such as heart disease and overweight because of complex aetiology, and large numbers of patients are necessary to establish both risk factors and treatment effect. Large-number cohort studies are

expensive and dependent on patient compliance. Registers give opportunities for large-scale epidemiological research and coupling of registers, thereby further increasing the possibility for identifying risk factors for illness [105]. Furthermore, health authorities are dependent on register-based surveillance of health as a basis for planning and dimensioning of the health service. This is true for hospital management, local health authorities and national health authorities. It is also used for economic reasons to calculate the hospitals refund.

Treatment of femoral neck fractures

History

The first available written description of a hip fracture was by the French surgeon Paré (1575). In 1850, the first attempt to repair a hip fracture using a nail was done by von Langenbeck. Later attempts were done with wooden screws or different metal nails or screws [106]. Poor mechanical stability, inadequate asepsis and unsatisfactory biocompatibility precluded a successful outcome. Therefore Kocher (1896) recommended resection of the femoral head. In the early 20th century, bed rest with traction for 6 months was the recommended way of treating hip fractures. However, many patients died of medical complications of inactivity such as pneumonia or emboli. In 1925, Smith-Petersen developed a nail and in 1931 he published the results demonstrating 75 % fracture union [107]. The nail was modified with cannulation to be inserted over a guide wire, thereby allowing insertion with less trauma under fluoroscopic control. Variations of the nail was used until the 1980s [108], when discussions went high between nail versus devices with lateral support for example sliding hip screw. At the same time the use of one or more cannulated screws won accept, and already in 1958 a Committee on Fractures and Traumatic Surgery published guidelines for the use of prosthetic replacement in the treatment of fresh femoral neck fractures [109].

Classification

Several classifications are used in the case of femoral neck fractures. However, none of these have acceptable inter/intra observer reliability [110-112]. Frihagen et al recommends simply to classify femoral neck fractures as displaced or undisplaced [113].

Surgical treatment

The first one to coin femoral neck fractures “the unsolved fracture” was Kellogg Speed in 1934 [114].

As late as in 2006, a Cochrane review concluded that. “There is insufficient evidence from randomised trials to determine whether replacement arthroplasty has any advantage over internal fixation for extra capsular hip fractures. Further larger well-designed randomised trials comparing arthroplasty versus internal fixation for the treatment of unstable fractures are required”.

Best treatment of dislocated, intracapsular (medial) hip fractures was controversial when the study leading to paper III took place [115-118]. Still there are two common surgical procedures performed: internal fixation and arthroplasty. Internal fixation usually implies two or three parallel screws inserted into the femoral neck through a small incision after closed reduction of the fracture. The procedure takes 15-30 minutes; the blood loss and traumatizing of tissue are minimal. Arthroplasty means either hemiarthroplasty or total hip arthroplasty. Hemiarthroplasty leaves acetabulum untouched and the joint will have metal against cartilage [119]. With total hip replacement the acetabulum will also receive an artificial joint surface. Arthroplasty surgery requires an extended surgical exposure, and blood loss and tissue trauma are larger than with internal fixation. Operating time for hemiarthroplasty increases to 45-75 minutes, more with total hip arthroplasty. Several studies comparing surgical methods are old, and the techniques used are no longer regarded as optimal [120-122]. The most recent studies, of higher quality than previous studies, indicate that short and intermediate time results are better with arthroplasty [123-127], even though absolute conclusions cannot be made. However, recent studies have shown that in short time there are more

reoperations in the group of internal fixation [123,128,129], and if patients previously operated with screws are reoperated with arthroplasty, the morbidity and costs increases [130]. Patients with dementia are usually excluded from studies [131,132], despite the fact that they represent a substantial part of patients admitted with hip fractures [19]. It is not clear whether arthroplasty or hip screws give the best long term results, e.g. more than one or two years after surgery [124].

How to compare results after surgical treatment

When comparing two different treatment methods, the outcome depends on the question asked and to whom. It is not certain that patient and doctor agree on the interpretation of a good result [133]. Patient-reported outcome measures (PROMs) are standardized and validated questionnaires that are completed by the patient [134] and designed to measure the patients perception of their own function and well-being. PROMs typically measure either the patients' general health ("generic" health status) or their health in relation to specific diseases or conditions. EQ 5-D is an example of a questionnaire aimed at measuring the patient's general health and it is divided into categories of mobility, self-care, usual activities, pain-discomfort, and anxiety-depression [135]. Harris Hip Score (HHS) and Oxford Hip Score are questionnaires aimed at measuring hip function [136]. PROMs are a critical component of assessing whether clinicians are improving the health of patients [137].

Differences in complications, morbidity, and mortality must be addressed when comparing treatments, both for the individual patients, and for society. In addition of being an acute problem that may imply a poor treatment result, complications also may lead to increased long term dependence for the patients, readmissions to hospital and increased cost [138-141]. Some complications, such as cement related illness and death, is such a rare occurrence that it is difficult to see differences between groups in standard sized clinical trials. Then larger trials, or trials with a particular focus on one outcome, or register studies, may be of value [142-144].

Furthermore, variables without interest to the single patient may still be important, e.g. cost of an implant or risk of dangerous exposure for the staff treating the patient. Vapour from bone cement is

an example. Studies indicate that cemented arthroplasty is the best choice for treating intracapsular fractures [144,145]. However, repeated exposure to bone cement is potentially harmful for the surgeon and the staff in the operating theatre [146-148]. The potential risk for the staff has to be balanced against the gain for the patient, and therefore cemented arthroplasties are widely used in Norway [144].

Timing of follow up is also important. A patient undergoing a large surgical procedure will probably report more pain the first days postoperatively compared to a patient with a minor procedure. After a year the results can be reversed. For many studies and conditions, the long term result is the most important. In a long term follow up study of spinal stenosis, the surgically treated patients did better for the first five years than the patients in the non-surgical group. The results were, however, identically after eight years[149]. For patients with long life expectancy, long term results are crucial for choice of treatment. For most hip fracture patients, the short term and intermediate term results are the most important. Early mobilization and pain relief is crucial to avoid complications and aids a fast recovery. Furthermore, the goal is to maintain independence and walking ability in the intermediate term (i.e. 1 to 5 years). Unlike elective hip arthroplasty for osteoarthritis, there is only a small subset of the relatively healthiest patients with femoral neck fractures where results after 10 and 20 years may be a concern when the treatment is selected, due to the short life time expectancy of hip fracture patients [150].

Aim of the studies

The main aims of the present thesis were to study the incidence of hip fractures in Oslo, Norway, to validate the data sources used and to study long term function of patients with a femoral neck fracture treated with the two most commonly applied surgical procedures

The detailed aims of paper I

- report the incidence of hip fractures in Oslo, Norway in 2007
- compare the hip fracture incidence with
 - historical data from Oslo
 - international data
- study reasons for changes in incidence

The detailed aims of paper II

- validate registers for the diagnosis of hip fracture
 - local hospital databases
 - Norwegian Patient Registry
 - Norwegian Hip Fracture Registry

The detailed aims of paper III

- Compare 5-year outcome after hemiarthroplasty and internal fixation in patients sustaining a femoral neck fracture with regard to
 - hip function
 - ADL-function
 - quality of life
 - complications/reoperations

Materials and Methods

Material and design paper I and II

Patients and population

All patients residing in Oslo who sustained a hip fracture during 2007 were included. To identify the patients, data were collected from the four somatic hospitals serving Oslo; Aker University Hospital, Akershus University Hospital, Diakonhjemmet Hospital, and Ullevål University Hospital. The fifth somatic hospital was not supposed to treat hip fractures, and by enquiry they made a database search and confirmed that none were treated. Only patients with a census registered address in Oslo were included. Exclusion criteria were patients with fracture distal to the lesser trochanter, with isolated fracture of the greater trochanter, or fracture due to cancer metastases. Patients with two different fractures within the observation period had both recorded. Patients admitted to more than one hospital for the same fracture were only recorded at the hospital where the primary surgery was performed.

Registers and databases

Hospital discharge registers

The hospitals electronic discharge registers were searched for patients discharged from Jan 1 2007 through Feb 1 2008 with the ICD-10 codes S72.0 or S72.1, cervical or trochanteric hip fractures as either main or additional diagnosis. The related diagnoses S72.2 (sub trochanteric fracture), S72.7, S72.9, T02.3, T02.5, T02.6, T02.7, T02.8, T02.9, and T12 were also reviewed to identify additional patients with a hip fracture. The chart of each individual patient was reviewed to confirm the diagnosis. In addition, the following information was registered: date of birth, national registration number, postal code, date of fracture, date of admission and hour, date of surgery, previous hip fractures, fracture classification (neck or trochanteric) and side, operation methods, ASA score, site of trauma (e.g. at home, nursing home, outdoors), and mechanism of trauma (e.g. low or high energy).

Hospital operation theatre protocols

The operation theatre protocols were reviewed to identify additional patients operated for hip fracture. In one hospital this protocol was electronic. In three hospitals they were written by hand. In three of the hospitals the protocols were the same as the operation planning program, and no patient was admitted to the operation theatre before the patient's name and diagnosis were written in the protocol. In the fourth hospital, surgeons registered the name after surgery was done. The additional fractures identified by operation theatre protocols were also confirmed by chart review.

Radiographs

In some cases, there was still doubt about the diagnosis after chart review. This was especially the case where operation method and description of the fracture did not match. In these cases, radiographs were reviewed to confirm the diagnosis and whether the fracture was trochanteric or in the neck region. These reviews were all done by an orthopaedic resident (RØS).

Gold standard for the number of hip fractures

In order to identify all fractures, both hospital discharge registers and operation theatre protocols were used to search for possible fracture patients. Medical chart, and if doubt radiographs, were searched in all patients identified with a possible fracture. Only patients with a verified fracture were included in the list of fractures, and this list was regarded as "the gold standard".

Statistics Norway

Population data for Oslo 01.01.2007 and demographic prognosis for Oslo until year 2030 were retrieved from Statistics Norway (SSB). The data were used for calculating gender- and age-specific rates of incidence of hip fractures in Oslo 2007 and to study the effect of the immigrant population.

Norwegian Patient Registry

A list of patients hospitalized from Jan 1. 2007 to Dec 31. 2007 discharged with the ICD-10 diagnosis (main or additional) S72.1 and S72.0 were retrieved from NPR. Only patients living in Oslo County were included. Additional diagnoses as well as NOMESCO codes were also retrieved.

Norwegian Prescription Database (NorPD)

The NorPD contains data on dispensed drugs in Norway. It contains the number of users, users per 1000 inhabitants and number of defined daily dose (DDD) of a particular drug or category, and can be split by sex, age and geography. Data in 2007 were anonymous and intended for research purposes. Reports are retrieved from their internet site[82].

Norwegian register on sale from wholesalers

The Norwegian register on sale from wholesalers is operated by the Norwegian Institute of Public Health. The purpose is to map total drug consumption in Norway for use by researchers and authorities in the main planning and control of supply of drugs. The statistics are based on the regulations concerning Drug Wholesale. Wholesaler-based drug statistics cover all sales of drugs from wholesalers to pharmacies, hospitals/nursing homes and non-pharmacy outlets with permission to sell drugs [151]. Drugs for humans and animals, both on prescription and over-the-counter, are included in the statistics. Drug statistics based on sales from wholesalers have been available in Norway since the 1970s and give an overview of long-term developments in drug consumption. Data are retrieved from annual reports published on their web site.

Norwegian Hip Fracture Register

List of all patients treated in one of the four hospitals in Oslo were retrieved from the Norwegian Hip Fracture Register. The entries in the register were compared with the gold standard [102].

Statistical methods

The level of statistical significance was set at 0.05. Results are given as mean (95% Confidence Interval (CI)) unless otherwise stated. Ratio statistic was used to compute confidence intervals for age. Two sample t-test or Mann-Whitney U test was used for comparisons between genders. NPar Test (Z approximation) was used to compare cervical and trochanteric fractures. Analyses were conducted using SPSS, PASW Statistics, except for calculating the confidence interval (CI) for age- and gender specific annual incidence rates, calculated as described by Armitage and Berry [91]. SPSS 18 was used for calculating incidence; SPSS 20 was used regarding register validity.

Effect of bisphosphonates

In Norway, prescription of bisphosphonates covered by public reimbursement was restricted to patients with established osteoporosis, requiring a T-score of ≤ -2.5 in addition to a low energy fracture. Of bisphosphonates prescribed in 2006, 98 % were covered by public reimbursement [24].

On this background, it was assumed that all users of bisphosphonates had osteoporosis.

The material of Falch and Meyer from Oslo 1996 [152] was used to estimate the number of individuals in Oslo with osteoporosis in each age group. This gave a proportion of females with osteoporosis (T-score ≤ -2.5) of 20 % in the age group 60-69 years and 28 % in the age group 70-79 years. According to Kanis et al [153], the risk of hip fractures among women with T-score ≤ -2.5 is 4.9 times higher in females aged 65 years (used for the age group 60-69 years) and 4.7 times higher in females aged 75 years (used for the age group 70-79 years), than those with T-score > -2.5 .

Furthermore, the use of bisphosphonates may reduce the risk of a hip fracture by 40 % [78], reducing the increased risk in treated osteoporotic women aged 60-69 years from 4.9 to 2.9 times higher, than in those with T-score > -2.5 , and from 4.7 to 2.8 in women aged 70-79 years. These figures were used to estimate the difference in risk between an untreated population and a population where 4% (all

with osteoporosis) of 60-69 years old women and 10% (all with osteoporosis) of 70-79 years old women used bisphosphonates.

The estimated decline in incidence due to use of bisphosphonates was compared with the observed decline in incidence in the respective age group in order to calculate the fraction of decline in incidence that bisphosphonate use may explain. Analysis on use in the age group >80 years was not possible due to lack of reference material, and analysis in the age group 50-59 years was not performed due to the small number of fractures.

Material and design paper III

Intervention

The study was carried out at Ullevål University Hospital (now Oslo University Hospital), Norway. Patients above 60 years with an intracapsular femoral neck fracture were assessed for inclusion. The resident on call included patients from the emergency department when they presented with a displaced intracapsular femoral neck fracture judged by angular displacement in either radiographic plane. Of 445 patients, 185 did not meet the inclusion criteria. Furthermore, 38 patients were not included because they refused to consent (31) or because the surgeon on call did not attempt to include the patient (4 patients) or the patient was operated elsewhere (3 patients). The patients were asked to participate in the study comparing the treatments internal fixation and hemiarthroplasty. Both surgical methods were in use in the department with choice of method based on the surgeon's preference before the study started. A total of 222 consecutive patients were included in the study. The inclusion period was from September 2002 to March 2004.

The patients were not eligible for inclusion if they were not ambulant prior to the fracture, were unfit for arthroplasty surgery according to the anaesthesiologist, had previous symptomatic hip pathology,

had a pathological fracture, if there was delay of more than 96 hours from injury to treatment, or if they lived outside the hospital's catchment area.

The randomisation was performed by placing 115 notes with the word "hemi" and 115 notes with the word "screws" in dense envelopes that were sealed and mixed before numbering. After inclusion, the resident on call opened the envelope with the lowest number. The surgery in the study was performed by the resident on call, as it would have been in a non-study setting making it valid for everyday practice.

Follow-up

Patients were seen in the outpatient clinic after four, 12, and 24 months, and after six years. At inclusion, the surgeon filled in data on retrospective pre-fracture Harris Hip Score (HHS) [136]. Furthermore, the ability to walk independently, place of residence, and comorbidity, including dementia were noted. At later visits, the same data were also registered. In addition, hip function, activity of daily living, and quality of life was assessed with questionnaires [138] at every scheduled visit. Complications and reoperations were also registered. The patients were asked not to inform the nurse and physiotherapist collecting the data about their treatment, and kept their clothes on to obtain blinding of the examiners. A chart review was performed of all originally included patients before the last follow up to record reoperations and other problems. The patients that were unable to come to the hospital were offered home visit or phone interview by a study nurse. At all visits, the patients had radiographs taken and had an appointment with an orthopaedic surgeon for a routine clinical follow up. These data were not used in the evaluation of the study patients. For patients not living at home, radiographs were taken at the institution where they lived.

Questionnaires

The EQ-5D questionnaire [135,154] was filled in by the patients. This is aimed at describing the patients' over-all health related quality of life, and can be used within a wide range of conditions. The patients are asked to assess how they regard themselves in 5 dimensions; mobility, self-care, usual

activities, pain/discomfort, and anxiety/depression. An EQ-5D health state may be converted to a single summary index by applying a formula that essentially attaches weights to each of the levels in each dimension [155]. This formula is based on the valuation of EQ-5D health states from general population samples. The patients are also asked to fill in their overall health on a Visual Analogue Scale (VAS) from 0 to 100, where 100 is best possible health ever.

Barthel Index questionnaire [156] was filled out by a study nurse blinded for the initial treatment. The purpose of the Barthel Index is to measure functional independence and need for assistance in mobility and self-care and it contains questions on basic activities of daily living (e.g., feeding, transfer, hygiene). The items chosen and the item weightings are based on the level of nursing care required and social acceptability and are rated in terms of whether individuals can perform activities independently, can perform with some assistance, or are dependent [157].

Harris Hip Score(HHS)[136] was examined by a study-physiotherapist blinded for the initial treatment. The HHS was published in 1969 and was developed for the assessment of the results of acetabular surgery. It intendeds to evaluate various hip disabilities and methods of treatment in an adult population. The domains covered are pain, function, deformity, and range of motion. The pain domain measures pain severity and its effect on activities and need for pain medication. The functional domain consists of daily activities (stair use, using public transportation, sitting, and managing shoes and socks) and gait (limp, support needed, and walking distance). Deformity takes into account hip flexion, adduction, internal rotation, and leg length discrepancy. Range of motion measures hip flexion, abduction, external and internal rotation, and adduction [158]. Best possible outcome is 100 points, covering pain (1 item, 0–44 points), function (7 items, 0–47 points), absence of deformity (1 item, 4 points), and range of motion (2 items, 5 points). The last part of HHS (range of motion) was not filled in due to difficulties with precise assessment. This is consistent with earlier studies, which find an excellent internal reliability of HHS except for deformity [159]. Maximum HHS is therefore 95 in paper III.

The higher the HHS, the less dysfunction a patient experiences. A total score of <70 is considered a poor result; 70–80 is considered fair, 80–90 is good, and 90–100 is an excellent result [136]. A ceiling effect of HHS is described[160] in well-functioning patients, but this is not the case for hip fracture patients [138].

Statistical methods

All analyses were conducted with IBM® SPSS® Statistics Version 19. All comparisons were made according to randomisation group, as defined by the “intention to treat” principle. Mann-Whitney U test was used for comparison between groups, and median and 95 % confidence intervals (CI) for median were used unless otherwise stated. T-test was used for comparison of mean values and Pearson chi-square was used for comparison of the dichotomous variable Barthel index score ≥ 95 %.

Ethical considerations

The studies were approved by the Regional Committee for Medical and Health Research Ethics (REC), South East Norway. REC is founded on the Norwegian law on research ethics and medical research. The committee is made up of people with different professional backgrounds, lay representatives and representatives for patient groups. The committees are appointed by the Ministry of Education and Research for a four-year term.

The epidemiological study (paper I and II) was approved by The Norwegian Data Protection Authority. Paper I, II and III were approved by the local Data Protection Official.

Modern medical research is based on informed consent. If informed consent is impossible to obtain, approval must be given from The Norwegian Directorate of Health. This approval was given for paper I and II. This approval was based on; 1) For the epidemiological study to be valid, all patients with a hip fracture had to be included, also the deceased. 2) After the patient was identified as having a hip fracture, the data were anonymized, thus the need of having an informed consent was not present at the time they would have been asked to give their consent. 3) Registering whether the person had a hip fracture the year before without any intervention was regarded as little intruding.

In the randomized study, paper III, all patients available to give informed consent did so. Were the patient was mentally impaired, a next of kin was consulted and the patient was included if it was thought to be in their own interest [161]. Both treatment options were regarded as standard treatment.

Main results

The incidence of hip fractures in women in Oslo has decreased significantly during the last decade, and is now at a lower level than in 1978/79. Although the diagnosis of hip fracture is unambiguously amongst clinicians, electronic diagnosis registers are inaccurate for this diagnosis.

Hemiarthroplasty has predictable and good long-term results after FNF and is the treatment of choice compared with internal fixation because of superior short time results with comparable long term results and less surgical complications.

Paper I

- The age adjusted fracture rates per 10,000 for the age group >50 years were 82.0 for women and 39.1 for men in 2007
- For the age group 50 years and older, the age- and gender-specific incidence rates of hip fractures for women in Oslo declined significantly not only during the last decade, but also compared with the rates reported in the late 1970s, with a reduction from 1996/97 to 2007 of 25 % and from 1978/79 to 2007 of 16 %.
- The reduction of hip fracture incidence seen in women was not evident among men.
- The fracture incidence in Oslo, Norway in 2007 is still higher than reported internationally in the same period.
- Bisphosphonates may explain up to 13 % of the total reduction in the age group 60-69 and up to 34 % of the total reduction in the age group 70-79 for women from 1996/97 to 2007.

Paper II

- Sensitivity of the hospitals diagnosis registers for the diagnosis of hip fracture varied between 95 % and 99 %. When sensitivity was calculated in total for all registers it was 98 %. The accuracy (PPV) was 86 % in total, and 64 %, 89 %, 96 %, and 96 % for the four different hospital diagnosis registers, respectively.
- NPR overestimated the number of fractures by 5 % when using the diagnose codes alone.
- The NHFR captured 69 % of the fractures compared with the gold standard. Sensitivity of the register was 29 %, 89 %, 54 %, and 77 % for the four different hospitals, respectively.

Paper III

- The recorded data on hip function, activity of daily living, and quality of life showed no difference between the randomization groups. Per protocol analyses did not change this.
- Twelve of the 31 patients randomized to IF still had their native hip joint. In the follow up period from two to six years, two patients, both in the IF group, were reoperated.

General Discussion

Hip fracture incidence

The age-adjusted hip fracture incidence has increased in Oslo over the two decades from 1978/79 to 1996/97 [33]. Paper I showed that the incidence is now decreasing and that it is significantly lower than in 1978/79 for women. The incidence rate for men is unchanged in the same period. The studies reporting the true incidence of hip fractures in Oslo have been conducted in the same way every decade from the first study in 1978/79 [33,92,93,162]. The studies are epidemiological cohort studies.

An epidemiological study on incidence is an observational study and not aimed at providing empirical evidence on for example risk factors, although it is highly relevant for making hypotheses on cause and effect. A prospective observational study would give the best information for that purpose. In paper I and II, the cohort was the population of Oslo which was studied for one year. Diagnosis and operation theatre protocols were real-time registered, and data were verified afterwards. There are some concerns when conducting a cohort study. From start it is the possibility for “zero time bias” or selection bias [163]. This occurs if the study population is different from the target population. Paper I includes the entire population of Oslo, and thus it describes the situation in Oslo well. However, the study might not be valid for the population of Norway, even less for Europe or other parts of the world. Accordingly, in Østfold county, only 50 km from Oslo, a decrease in hip fracture incidence could not be confirmed in the decade from 1998-2003 to 2008-2010 [164]. This indicates that there are differences between the population of Oslo and Østfold regarding risk of hip fracture, and it stresses that results from a study is only valid for the actual population. On the other side, this gives an opportunity to make hypotheses about the influence of different risk factors by studying the differences between the two populations.

Hip fracture as a marker of osteoporosis

Hip fracture incidence is a useful surrogate for determining the burden of osteoporosis. Furthermore, changes in specific risk factors for osteoporosis can explain the changes in hip fracture incidence in addition to effective treatment.

Nutrition throughout life affects bone health [165]. Even birth weight is correlated with bone mineral density (BMD) later in life [166]. This is thought to be a result of intrauterine programming under which endocrine responses are adjusted to nutrition during pregnancy. Data on changes in birth weight in Norway in early twentieth century are not available. The improved standard of living in this period may however imply better nutrition during pregnancy with the likely effect of increased birth weight compared to those being born during World War I, thereby having an effect on peak bone mass in this population. The median age of female hip fracture patients in 2007 was 85 years. Hence, many of the patients were born in the 1920s and were children and adolescents during the 1930s and 1940s. This concurs with the end of the demographic transition in Norway, when both death rates and birth rates were falling due to a rise in standard of living [167]. Better nutrition in childhood and adolescence would further contribute to a raise in peak bone mass [168]. In adult age, nutritional factors will still affect bone health. It is widely accepted that adequate intake of calcium and vitamin D are required to maintain good bone health as well as the intake of proteins and other vitamins[165]. On the other hand, smoking and alcohol have the opposite effect [169,170]. Studies on changes in dietary habits or smoking and alcohol use in the elderly are unfortunately not available in Norway for the decades studied.

Low body mass index (BMI) is a known risk factor for hip fracture, partly due to the effect on BMD, but the lack of fat padding over the trochanteric region could also increase the risk. The risk doubles with a drop in BMI from 25 to 20 (upper and lower normal values). An increase above 25 is, however, not associated with a decrease in hip fracture rate to the same extent [171]. A substantial increase in

BMI has been observed in the adult Norwegian population [172], which might contribute to the decreasing incidence of hip fracture. Data on the elderly is not readily available, but self-reported anthropometric data from national health surveys in 1998 and 2008 revealed no change in BMI [173,174].

Because of immigration, the demographic changes in Oslo during the last decade have been considerable. The percentage of men over 50 years from outside Europe and North America has increased from 6 % in 1998 to 11 % in 2008 [167]. For women the corresponding increase was from 3 % to 8 % [167]. Sensitivity analyses indicate that the lower incidence of hip fractures in persons from outside Europe is unlikely to be a major reason for the reduction of incidence rate. This is due to the age distribution of the immigrant population where few have yet reached older age, also reported by Lofthus et al on distal forearm fractures in Oslo [90].

Effect of treatment of osteoporosis on incidence

Changes in the use of bisphosphonates and hormone replacement therapy (HRT) in the population at risk may also have contributed to changes in the incidence of fractures. Bisphosphonates were introduced to the Norwegian market in 1996, and use before 1996/97 is therefore negligible. Paper I estimated that use of bisphosphonates can explain 13 % - 34 % of the total reduction in hip fracture incidence in women in the age group 60-69 and 70-79, respectively, from 1996/97 to 2007.

The effect of HRT on reducing osteoporotic fractures is strongest when use is closest in time, and 5 years after discontinuation the effect is negligible [175]. Meyer et al estimated that half the reduction in forearm fractures in young postmenopausal women in Oslo in the period from the 1970s to 1990s was due to use of HRT [176,177]. In the three years before 1997 an average of 12000 DDD/year of HRT were sold according to the register on sale from wholesalers. Ten years later the corresponding number was 8500. The reduced use of HRT in the last decade might in fact therefore counteract the decrease in hip fracture incidence rather than be part of the explanation.

Epidemiological studies can give rise to hypotheses about risk factors by comparing different regions, but historic comparisons may be even more valuable as the changes in risk factors can be easier to identify. Paper I shows a significant decrease in hip fracture incidence. The observed decrease in incidence in Oslo corresponds with other recent reports from western countries [178,179] as well as a study from Norway [180]. Other authors conclude that the reason for the reduced incidence remains unknown. The effect of bisphosphonate treatment was calculated and it might explain some of the decrease in fracture incidence. This is consistent with findings from United States [178].

Healthier geriatric population

The lack of identifiable changes in risk factors for hip fracture, combined with the significant decrease in incidence, may point to the largest risk factor of hip fracture; age. This is generally considered a non-modifiable risk factor. However, as hip fracture incidence increases exponentially with age, a healthier geriatric population with younger biological than chronological age might result in a decrease in the age-adjusted hip fracture incidence. Moe and Hagen actually found that elderly are getting healthier [181]. They found that both functional limitations-free and disability-free life expectancy appeared to have increased more than total life expectancy at age 67 during the last 20 years (1987-2008). Other age-dependent diseases have also decreased in incidence, e.g. myocardial infarction [182]. Perhaps the decline in age-adjusted incidence of hip fracture is a marker indicating that the geriatric population is getting healthier. However, the increased number of elderly persons, as well as a possible increase in hip fracture in men, will account for an increase in total number of hip fractures in the near future [183-185].

International comparison

Earlier studies [33,92,93,186] have demonstrated that hip fracture incidence in Oslo, Norway, is the highest reported worldwide. A study by IOF working Group on Epidemiology and Quality of Life showed that there is a greater than 10 fold variation in hip fracture risk and fracture probability between countries [87].

Figure 3. Hip fracture rates for men and women in different countries. Where estimates are available, countries are colour-coded *red* (annual incidence >250/100,000), *orange* (150–250/100,000) or *green* (<150/100,000). Reprinted from Kanis et al 2012 [87]

The general impression is that the northern European countries have the highest incidence of hip fracture and that North America, Australia, and Russia are at intermediate incidence. Low incidence is found in Africa, Asia, and South America (except Argentina) [87,187]. In Asia, there are, however, reports on increasing incidence [188], and Japan, South Korea and Thailand are regarded medium incidence by the International Osteoporosis Foundation [189]. Low incidence is to some extent associated with poor health care system. The Northern European countries have well developed systems for registration of patients; on the other hand the best incidence study in South Africa is from the Bantu population conducted in 1968. It is therefore difficult to know if the low incidence rates are attributable to the methods used, i.e. poor register and/or data collection quality or patients treated conservatively at home and never reaching hospital [187,188]. Schwartz et al carried out a cross-national study in 1990-1992 in five different geographical locations to study this issue [190]. Using hospital discharge registers, operation theatre protocols, radiology logs and medical records, they identified cases of hip fractures in patient aged 20 years and older. They found that

incidence rates varied widely between locations, Beijing reported the lowest rates and Reykjavik the highest. The additional cases found in operation theatre protocols and radiology logs increased the number of fractures by 11 % to 62 %. The final estimates of hip fracture incidence, taking into account all studied sources, ranged from 15 % lower to 89 % higher than an estimate based on hospital discharge registers alone. However, Schwartz et al also found that the over- and underestimation when using hospital discharge registers to estimate incidence of hip fracture is smaller than the larger differences reported among different countries. This indicates that although the validity of the registers used are of great importance, there are true differences among countries regarding hip fracture incidence rates. The differences between countries can be due to different race indicated by similar rates in UK and in Ontario, Canada where the population is predominantly of English ancestry. Consistent with this, the Mexican and Spanish rates are comparable, probably due to the common genetic background [191].

The worldwide variation of hip fracture incidence allows for speculations on risk factors for hip fracture and osteoporosis. Interestingly, the occurrence of osteoporosis is higher in urban than rural areas – in Norway [89] and the opposite in Iran [192]. Both studies showed that BMI was part of the explanation. The Iranian study also showed that low educational level was a risk factor for osteoporosis, as is also reported in other studies from Asia [193]. Low education is probably associated with inadequate nutritional intake. Exposure to sunlight and thus level of vit D is, however, higher in persons with low education [192]. Risk factors of osteoporosis are multifactorial. Epidemiological studies can contribute to deduce hypothesis that can be tested to establish better preventive measures and treatment for osteoporosis.

Validity of data registers

Epidemiological studies on incidence are widely used as basis for research, health care administration, preventive measurements etc. Valid registers are necessary for true conclusions to be drawn. As the incidence rate is calculated with the number of incidents as numerator and the

population where incidents are studied as denominator, the true value of the denominator is of great importance for a precise incidence. In western countries, there are well maintained registers of residents. In some countries, however, residence information has to be obtained from voter registers or for example register of driver licences. These registers are not as complete as compulsory national registers. Another important dependency for making an incidence estimate is the possibility to isolate a geographical area. In Oslo, all patients are referred to one of three (in 2007 four) somatic hospitals. Only patients traveling to another geographical area at the time of the fracture would have surgery in another hospital. However, the chance of the patient being transferred to their home hospital before discharge, or attending outpatient clinic at their home hospital, is very high. Other places in the world, the catchment population of a single hospital is not so well defined, making it more difficult to identify all the patients with a hip fracture in one defined geographical area.

The correct numerator, the number of new incidents, is, however, often the most difficult to obtain. Data registers are used for this purpose. In study III, the inaccuracy of data registers are documented. The present results are consistent with previous findings [190].

Why are the registers inaccurate?

Different registers have different sources of error. The NPR is based on the hospital diagnosis registers. The discrepancies between the two registers are difficult to explain, errors of data transfer, either personal or electronic are possible. The hospitals' diagnosis registers are based on manual registration of diagnoses and procedure codes. First of all, a correct diagnosis has to be made. The diagnosis of a new hip fracture is unambiguous. However, the hip fracture may not be the patient's largest problem, and may thus, correctly, not be coded as the main diagnosis. A patient treated for a hip fracture that was complicated with pneumonia and sepsis, perhaps treated for a long time in an intensive care unit because of the infection, could have pneumonia as the main diagnosis at discharge. The hip fracture should then be registered as an additional diagnosis. If the diagnosis system was used correctly, this would not be a problem because both main and additional diagnoses

of a new hip fracture would be included in a register based, epidemiological study. What paper II showed was, however, that the diagnosis of a new hip fracture (ICD-10 S72.0 or S72.1) was wrongly used as an additional diagnosis when for instance the patients were hospitalized for other reasons. In this case “T93.1 Sequelae of fracture of femur” is the correct diagnose. T93.1 also applies to patients admitted for removal of implanted hardware after a hip fracture. In paper II, several of the patients admitted for hardware removal surgery were given the diagnosis S72.x, which should only be used for an acute fracture. Better education of, or reimbursement for, doctors in the use of ICD-10 classification and/or trained staff going through the diagnosis-codes before they are entered into the registers, would improve register quality. In addition to Lofthus et al [186], two studies on validation of hip fracture diagnose in NPR has earlier been published [194,195]. Emaus et al. showed that during seven years, it was not consistent whether the number of hip fractures was over- or underreported to NPR. This may, for epidemiological studies, lead to a too high or too low incidence, and efforts to prevent hip fractures in the population could wrongly be regarded as efficient or inefficient. For planning of health care, an overestimation could lead to overstaffing and use of resources that could have been used on other groups of patients. The study from Høiberg et al retrieved samples from NPR and did chart review to verify the fractures. By combining diagnosis and procedure codes they found that the accuracy was 98 %. However, by using the diagnosis code alone, only 74 of 307 (24 %) entries were true fractures.

The quality registers have other sources of inaccuracy. The NHFR are dependent on patient consent as well as surgeon or hospital compliance to achieve register completeness. Surgeons’ compliance is probably the main reason why 30 % of the patients were not reported to NHFR in 2007. Likely explanations might be lack of attention to the relatively new register, young and inexperienced colleagues performing the surgeries, and surgeries performed on busy shifts by the resident on call. One can, however, not ignore the possibility that specific patients were not reported, e.g. patients with expected worse outcome, if the surgeon was insecure of later use of the register.

Consequences of inaccurate registers

NPR is the Norwegian nationwide register. It is used as a basis for a nationwide publication of quality indicators of the different hospitals [196], and comparison between hospitals is dependent on high data register quality. Regarding treatment of hip fractures; Hip fractures operated within 48 hours and 30 days mortality after hip fracture are two of 25 indicators reported. Mortality the first year after fracture is significantly higher than in the general population [18,197], and registration of other patients as acute hip fracture patients will probably make the hospital look better regarding 30 days mortality. In the present study, one of the hospitals overestimated the number of patients to NPR by 18 %, and one of the other underestimated by 12 %. This means that data from NPR is not sufficient for comparing quality of individual hospitals because it is not the same patient population that is reported.

Quality registers describe disease patterns and treatment choices, and more accurate registration gives a more accurate description. Registers are, however, increasingly used to identify associations between exposure factors, e.g. treatment, and outcome. If the register is not valid, wrong conclusions can be made. Data errors can be divided into systematic (type I) errors or random (type II) errors [198]. The random errors will be minimized when numbers of entries increases. The systematic errors will not disappear with increasing number. Systematic errors will lead to wrong conclusions. For example if the difficult fractures are not reported, a surgical device suited only for simple fractures will look better in what is assumed to be the total population of hip fracture patients. In randomized controlled trials, however, the population studied are well defined, and the reader can decide if the study results are valid for his or her patient. The generalizability of a register study is often difficult to determine, and a large number of entries make impressive tables and small confidence intervals, and the wrong conclusions are more prone to make an impact on practice. In paper III, the patients included in the NHFR were younger than the total population, and one could assume that they were also healthier. This means that the register data from NHFR might not be generalizable to the hip fracture population. Looking at the reoperation rate in hip fracture patients

operated with HA or IF, a randomized trial by Frihagen [18] found 40 % vs 10 % reoperations while a register study from NHFR [199] found 23 % vs 3 %, respectively. This indicates that register studies are not sufficient to support clinical practice in medical conditions that are common enough to conduct randomized controlled trials.

Treatment of femoral neck fractures

Medicine is based on science and has empirical support for the decisions made. The term Evidence based medicine (EBM) intends to take this further. Only evidence from well conducted studies can yield strong recommendations [200]. The term EBM was initially used to describe a method of teaching medicine, but is now used in every level of health care. The opposite of EBM as basis for medical choices is expert opinion/single practitioner's belief.

EBM uses a pyramid of evidence to describe the quality of scientific recommendations regarding treatment of illness. Systematic reviews based on high-quality single studies are on top of the information hierarchy.

Figure 4. EBM Pyramid 2006. Trustees of Dartmouth College and Yale University.

Randomized Controlled Trials represent the highest level of evidence for single studies. It is also important that the studies are blinded if possible. Study III was conducted as a single blinded randomized controlled trial. It was neither possible nor desirable to blind the patient regarding treatment. To be able to do so, the patients that were treated with IF had to get a much larger operating incision than necessary to make it similar to the HA-patients. In addition, all patients would have to have the same restriction as HA-patients for all the period after surgery (don't cross the legs, be careful about forward bowing). This could in turn take away the possible advantage of no restrictions in the IF-group. It was regarded more important that the patient received what was standard treatment after the specific surgery, than blinding of the patients. Furthermore, very few patients would have a bias to one or the other treatment, although nursing staff or physiotherapists is a possible source for biases during rehabilitation if they had a preferred treatment method.

A randomized controlled trial with sufficient power has one main limitation: The study population. Many studies have narrow inclusion criteria. There is a risk that the results may be used for other patient categories as well because of lack of data on sub-populations with the same diagnosis[201]. Study III has attempted to include all patients presenting with a displaced femoral neck fracture aged 60 years and older in a Norwegian area-hospital. Mentally impaired patients were also included, as they are a substantial part of the hip fracture population [19,202]. Of the patients admitted to the hospital in the inclusion period, only 1% of the patients were not attempted to be included. Twelve percent refused consent, resulting in inclusion of 87% of the patients admitted to the hospital in the inclusion period. The study population was therefore likely to be the same as the general hip fracture patient population in Norway, and the results will probably have a high generalizability. Another objection to randomized trials is if the intervention is different to what is offered to the general patient. A lot of studies are so-called expert studies. An example is "The HEALTH study", comparing Total hip arthroplasty and hemi-arthroplasty where surgery are to be performed by a skilled arthroplasty surgeon[203]. At least in Norwegian practice, a hip fracture patient is operated by the resident on call. If the results of a trial using only expert surgeons are applied on everyday practice in

hospitals where surgeons without special expertise operate, this could alter the outcome. One example may be the complication of hip dislocations after arthroplasty surgery. In expert hands on selected patients the dislocation rate may be zero [132,204], but when the surgery is performed by surgeons in training and surgeons who are not expert arthroplasty surgeons the dislocation rate is almost always higher, up to 22 % [125]. The results from paper III are transferable to the general hip fracture patient in Norway. However, subgroups are not studied and possible variations in results according to functional level or morbidity will not be caught in this broad-based study.

The initial power analysis did not take into account the mortality of hip fracture patients for 6 years duration of the study. A post-hoc power analysis shows that with the actual standard deviations and number of patients, the difference in HHS had to be at least 19 of 95 to detect a difference. As a 10 point difference is regarded clinically relevant, the study did not have enough power to detect clinically relevant differences between the two groups at 6 years.

In one year, 25 % of the patients with a hip fracture are deceased. After 6 years, only one third of the patients are still alive [205]. Paper III demonstrated a tendency towards higher mortality during the first months after fracture for patients treated with hemiarthroplasty compared with internal fixation. The long and medium term mortality were, however, equal in the two groups. This has also been indicated in register studies [199]. The surgical burden of a hemiarthroplasty may be higher for the patient compared with internal fixation. This may explain a difference in early mortality [206]. Several randomized studies have also reported a non-significant tendency towards a higher mortality after hemiarthroplasty [125,207]. If there is a difference in mortality between the methods, it would be an important factor in the decision making, even when including the functional benefits of treatment with hemiarthroplasty. It would, however, require a very large study to conclude on this matter; Bhandari et al [125] have estimated that demonstrating a 5 % increased mortality rate will require a study sample size of 26 641 patients.

The median survival time after a hip fracture is 2.6 years for men and 4.2 years for women [197]. It is thus useful to distinguish between the patients with long and short life expectancy when selecting surgical treatment. This can be a challenge, but sex, age, pre-fracture functional level, and medical comorbidity can be of use [208]. In paper III, there were demographic differences between patients that died within the first six years following fracture, and the one third that still were alive after six years. The patients that died were older at inclusion and had a higher ASA (American Society of Anesthesiology) score. The difference was more pronounced in men, which may be explained by a possible difference in pathogenesis of hip fracture in men and women [209]. The patients with short life expectancy need a treatment that gives immediate good function. Hemiarthroplasty has shown to be superior, regarding functional outcome, to hip joint retaining devices such as screws [207,210,211].

After implantation of a prosthesis, the broken bone is removed and fracture healing is no longer required. The soft tissue is left to heal, but this process is faster, and in the case of femoral neck fractures, more reliable than fracture healing. Frequent complications reported are peri-prosthetic fracture, aseptic loosening and dislocations. However, the main challenge with hemiarthroplasty is infection [144,212]. The rate of infection in patients undergoing HA following hip fracture is approximately 5 % [213]. Measures to further reduce this rate have until now not proven effective [214].

The femoral stem can be fixed in the femur either by press fit (uncemented) or by the use of bone cement [144]. The uncemented stems save some time in the operating theatre, and there are studies showing equal results after 1 year [212]. However, the reports of the same cohort after 5 years showed a high risk of periprosthetic fractures in the uncemented stems [145], and both register data [144] and metaanalysis indicate inferior results in uncemented hemiarthroplasty [215]. Most studies with uncemented arthroplasties, however, use older arthroplasty models. Modern uncemented

femoral stems with anatomical or canal filling designs with surfaces that adhere quickly to the surrounding bone may perform better. Until studies with comparable results for cemented and uncemented hemiarthroplasties in hip fracture patients are published, cemented arthroplasties should be the treatment of choice.

Healthier geriatric population – longevity – total hip arthroplasty

Of the two commonly used surgical procedures after hip fracture, HA is superior to IF with two parallel screws [205,216,217]. Other variations of IF include different screw designs, the use of three or four screws, the use of pins, and use of screw/plate combinations. A Cochrane review found no evidence that one is better than the other [218]. Recent biomechanical studies indicate that locking devices might improve fracture stability, but clinical studies are mandatory to find out if this is true in the clinical setting [219,220]. Younger patients are treated with IF because of the risk of prosthetic wear. This is probably the group where improvements in internal fixation devices will be of advantage because of the good results of arthroplasty in the elderly.

As HA has been demonstrated to be superior to IF for treating hip fractures, other treatment options should be compared with HA. In hip osteoarthritis, treatment with HA has shown inferior results compared with THR [207,221]. This could be due to the pre-existing acetabular wear in patients with osteoarthritis. In one study, only 20 % of the patients with osteoarthritis treated with HA had excellent results after mean follow up 4 years [222], compared with 95 % after THR [223]. However, THR leads to prolonged surgical time, additional blood loss and excess costs of implants compared with HA. While this is an important issue in fragile patients, it is probably not a major concern in the healthier patients. A Cochrane review concluded that a majority of relatively young and healthy patients with femoral neck fractures had significantly less residual pain and better function at one, two and four years after fracture with THR than with HA [215]. There were, however, increased risk of dislocation and increased surgical time. A cost effectiveness analysis concluded that it is likely that THR is associated with increased costs in the initial two-year period, but the long-term costs favour

THR due to lower revision rates [224]. It still remains unclear which patients that will profit on having a total hip replacement instead of hemiarthroplasty after a femoral neck fracture.

Main Conclusion

The incidence of hip fractures for women in Oslo has been declining over the last 30 years after an initial increase. For men, however, the incidence has been unchanged. The incidence is still the highest reported in the world.

The local hospital databases have a high sensitivity and can be used to identify possible cases. The accuracy is lower. The unpredictable degree of both over- and underestimation in the different registers makes it difficult to apply correction algorithms to improve data quality.

Hemiarthroplasty has predictable and good long-term results after femoral neck fractures regarding hip function, ADL-function, and Quality of Life assessment. Hemiarthroplasty is the treatment of choice compared with internal fixation.

Further Research

Hip fracture incidence is a surrogate for the burden of osteoporosis in the community and repeatedly registrations of hip fracture incidence is helpful for planning the health care for this patient group as well as evaluate effect of preventive measurements. At best, the temporal and geographical variations in incidence may help elucidate the causes of hip fractures and aid the prevention. As the registers are unpredictable in over- and underestimating the true incidence, repeated research with a consistent methodology is important.

Arthroplasty is established as the treatment of choice in femoral neck fractures in the elderly, and further research should focus on type of arthroplasty. One important question is whether to use hemiarthroplasty, as in the present study, or to elucidate if subgroups of patients would benefit from total hip arthroplasty. Other questions that merit further attention are whether to cement the arthroplasty in place and what surgical approaches might be advantageous. It is likely that different solutions may be best for different subgroups of patients, and that an algorithm based on functional demands, comorbidities, and the risk of complications may be developed to assist in deciding the individual treatment.

Furthermore, hip fracture patients are prone to perioperative complications and death. Research on how to optimize the complimentary, non-surgical treatment will be of great value, and integrated multidisciplinary care (e.g. with geriatric, anaesthesiologic and orthopaedic input) both pre-, peri- and postoperatively seems to be the most promising way forward [225].

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Papers I-III

Errata

Name of candidate: Ragnhild Øydna Støen

Title of the thesis: Hip fracture epidemiology and treatment

Six references were duplicates. They are deleted and the following references are corrected.

Side	Reference	Original text	Corrected text
58	25	Avdeling for primærhelsetjenester. Faglige retningslinjer for forebygging og behandling av osteoporose og osteoporotiske brudd. IS-1322, 1-83. 2005a. Sosial- og helsedirektoratet. Ref Type: Report	Erased, replaced in the thesis text with reference 1
67	155	Black D M, Thompson D E, Bauer D C, Ensrud K, Musliner T, Hochberg M C, Nevitt M C, Suryawanshi S, Cummings S R. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. FIT Research Group. J Clin Endocrinol Metab 2000b; 85(11): 4118-4124.	Erased, replaced in the thesis text with former reference 79, number 78 in corrected manuscript
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67	158	Tidermark J, Bergstrom G, Svensson O, Tornkvist H, Ponzer S. Responsiveness of the EuroQol (EQ 5-D) and the SF-36 in elderly patients with displaced femoral neck fractures. Qual Life Res 2003a; 12(8): 1069-1079.	Erased, replaced in the thesis text with former reference 136, number 135 in corrected manuscript
67	162	Harris W H. Traumatic arthritis of the hip after dislocation and acetabular fractures: treatment by mold arthroplasty. An end-result study using a new method of result evaluation. J Bone Joint Surg Am 1969a; 51(4): 737-755	Erased, replaced in the thesis text with former reference 137, number 136 in corrected manuscript
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