On prevention of second hip fracture surgery

epidemiological and biomechanical aspects of elastomer femoroplasty

T.J. van der Steenhoven

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To my family

CONTENTS

CHAPTER 1

General introduction and outline of the thesis

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

Hip fracture incidence

Osteoporotic fractures in elderly patients have become a major burden on public health resources [1]. Recent epidemiological studies report lifetime risks of any fracture of the hip, spine, and forearm of around 40% for women and 13% for men [2]. In 2010, approximately 2.5 million new osteoporotic fractures occurred in Europe's largest countries (France, Germany, Italy, Spain, UK) alone [2]. Of these fractures, the hip fracture and subsequent hip fracture surgery have the most devastating impact on a patients' life, with repercussions that extend beyond the traumatic injury into the domains of medicine, rehabilitation, psychiatry, social work, and health care economics [3, 4].

In the Netherlands, between 2000 and 2004, an average of 17,000 patients with a hip fracture were admitted per year [5]. Between 2009 and 2011 this average number was 19,700 patients [6]. An increase of 16% in hip fracture incidence over a period of 10 years. With demographic changes and increasing life expectancy in industrialized countries, a doubling of the incidence of hip fractures can be expected by the year 2050. By that time the worldwide incidence is estimated to reach a staggering 6.3 million hip fractures per year [7, 8].

Sequelae of hip fracture surgery

Hip fracture surgery is associated with high morbidity and mortality. In the first 3 months after surgery, the mortality risk is increased five- to eight-fold [9, 10] – an excess risk that might persist for several years thereafter [11, 12]. The one-year mortality rate after hip fracture surgery can be as high as 32% [10]. Many patients – particularly those with mental illness, coexisting medical conditions and those suffering from postoperative complications – have a permanent reduction in activities of daily living and require postoperative discharge to an institutional care facility [13-16]. Half of all hip fracture patients will never recover to their pre-fracture functional capacity and 25% of these patients reside in a long-term care institution, 1 year after sustaining a hip fracture [9–11[16]].

The costs of hip fracture surgery have a considerable impact on healthcare resources. Elderly patients aged 65 years and over, especially women, consume a disproportionate share of the trauma care budged, mainly caused by hip fractures [17]. The total cost in the USA, including the operation, in the first year after hip fracture surgery is US $ 26,000 per patient, [18] and the lifetime attributable cost of a hip fracture is calculated at US $ 81,300, of which nearly half (44%) is related to nursing facility expenses [19]. In the Netherlands, the total amount spent on hospital costs of

patients with hip fractures is approximately € 500 million per year. (*RIVM Kosten van Ziekten database 2013, www.kostenvanziekten.nl).*

Second, contralateral hip fractures

Of those patients who survive the first fracture, up to 16% subsequently sustain a fracture on the contralateral side [20-22]. Taking previous predictions on future hip fracture incidence in account, the worldwide number of second hip fractures by 2050 could well exceed 1 million per year. In contrast to the extensive documentation on the impact of first hip fracture surgery, the consequences of second, contralateral hip fracture surgery on the disability of these frail patients remain largely unknown. Limited data suggest that patients with a second hip fracture might have worse mobility shortly after the surgery compared to patients with a first fracture [23-25]. In a recent study of patients with a sequential hip fracture, the second injury was associated with greater loss of independent mobility and changes in residential status compared with single fractures at one-year follow-up [26]. Furthermore, in a cohort of 5,341 patients, Sawalha et al reported a significantly higher mortality rate, one year after a second hip fracture (31.6% vs 27.3%, *P*= 0.024) [27].

Prevention of first and second hip fractures

Given the detrimental impact of hip fractures on elderly patients, first and secondary fracture prevention efforts are clinically justified. Preventive measures thus far have been aimed at (1) the prevention of falling and (2) the prevention of fracture after falling.

Fall prevention programs show a significant reduction in fall incidence and could therefore be a valuable new tool to improve mobility and independence of individuals with osteoporosis [28]. Training fall arrest strategies, such as martial arts fall techniques, could be useful to prevent hip fractures in persons with osteoporosis [29]. Of the existing balance exercises, Tai Chi Chuan has proved to be the most successful in decreasing falls [30, 31]. However, all fall prevention strategies can only be implemented provided that the training itself is safe. Future randomized trials among the elderly, octo- and nonagenarians, should examine the efficacy and safety of these fall prevention programs.

Fracture prevention by treating osteoporosis medically, has shown its positive effect in multiple randomized trials [32, 33]. However, a considerable number of patients who have sustained one hip fracture do not receive adequate pharmaceutical treatment for osteoporosis [34]. Poor compliance with oral bisphosphonate therapy and the short time between first and second fracture have been shown to diminish its efficacy [35]. Therefore, alternative approaches have been developed for frail patients at particular risk of acquiring a second, contralateral hip fracture (i.e. older age with

weakened motor skills, visual impairment, dementia, respiratory disease or solitary life after first hip fracture). One example is a hip protector. This device offers an external mechanical protection with either hard-shell or silicone pads in the region of the greater trochanter [36]. However, compliance with the device in non-institutionalized patients at risk of a second hip fracture, remains a concern. Shock absorbing floors to prevent fall related injuries in permanent care facilities or in hospital geriatric wards have the potential of being cost effective but further research is needed to establish their efficacy [37]. Airbags to wear around the belt are currently being developed and under investigation. Prevention of fracture by cement femoroplasty has been suggested [38, 39]. Although, biomechanical cadaver experiments showed promising results on increased load to fracture, cement femoroplasty has some major drawbacks. The high temperatures of curing bone cement could cause osteonecrosis. Moreover, fractures that occur after a failed preventive cement femoroplasty are potentially more difficult to treat, comparable to peri-prosthetic fractures [40-42].

However, despite all these efforts and the introduction of the above-mentioned preventive measures, the overall incidence of first and second hip fractures has not decreased in the last decades [43, 44].

Aim of the thesis

The aim of this thesis is twofold:
1. Explore the prevalence and sequelae of second hip fractures in two areas in the Netherlands, and
2. Make a biomechanical and biocompatibility evaluation of elastomer femoroplasty (EF), a minimal invasive technique to potentially prevent hip fracture surgery.

Outline of the thesis

Part 1: Sequelae of second hip fracture surgery

In part one, we aim to evaluate the prevalence of second proximal femur fractures and the sequelae of consequent hip fracture surgery. In ***Chapter 2 and 3*** we elaborate on the incidence of second hip fractures, the variation in fracture types and fracture treatment, complication rate and postoperative institutionalization after hip fracture surgery.

Part 2: Elastomer Femoroplasty

In part two, we propose a minimally invasive technique to prevent the potentially devastating sequelae of a second hip fracture. This new technique, elastomer femoroplasty (EF) is mechanically evaluated in an ex-vivo model. ***Chapter 4*** introduces

the operative technique of EF as a preventive modality to prevent contralateral hip fractures after ipsilateral hip fracture surgery. In ***Chapters 5 – 8*** the feasibility of EF in an in vivo cadaveric biomechanical experiment is evaluated. In ***Chapter 9*** we discuss the thrombogenicity, a major issue in biocompatibility, of the elastomer used for the proposed preventive femoroplasty

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PART I

Sequelae of second hip fracture surgery

CHAPTER 2

A retrospective analysis of bilateral fractures during a 16-year period: localization and variation in treatment of second hip fractures

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ABSTRACT

Evaluation of subsequent contralateral hip fractures was the aim of this study. For this retrospective analysis patients were selected from the database of the LUMC, a teaching hospital in the southwest of the Netherlands. We analyzed all patients with subsequent hip fractures between 1992 and 2007. Exclusion criteria were high impact trauma and patients with diseases or medication known to have a negative effect on bone metabolism.

A total of 1,604 hip fractures were identified. Possible predictive factors for the second fracture and descriptive statistics related to surgery were recorded (Hb and HT before and after the operation, total amount of intra- and postoperative blood loss, type of surgical treatment (implant), complications, time of death after the last fracture, time between arrival in the hospital and operation and hospital stay for both fractures). A total of 32 second hip fractures were identified (2%) at a mean of 27.5 (SD 28.9) months after the initial hip fracture. The mean age at the first fracture was 77.2 years (SD 11.7), and 27 of 32 patients were female. Of these 32 patients (64 bilateral hip fractures), 32 fractures were intracapsular (1 femoral neck, 31 sub capital) and 32 were extracapsular fractures (6 subtrochanteric, 26 transtrochanteric). Although 24 of the 32 patients had identical first and second hip fractures, only eight out of 24 patients were treated with the identical implants.

There was a significant difference in Singh index between both hips at the time of the first fracture. There was also a significant difference in Singh index between the hip that was not broken at the time of the first hip fracture compared to itself after the second fracture. All other studied patient and fracture characteristics were not significantly different.

In this population the percentage of second hip fractures was relatively low compared to other studies. The choice of implants in this study shows that implants were chosen randomly. Because there is a significant difference in Singh index during first and second hip fracture, osteoporosis medication might reduce the incidence of second hip fractures.

INTRODUCTION

The lifetime risk of sustaining a hip fracture is 17.5% in women and 6.0% in men [1]. Complications of hip fracture and consequent hip fracture surgery include death, disability, long-term care needs and loss of social independency [2]. Following hip fracture surgery, there is a one-year mortality rate up to 36% over the subsequent year. Half of the patients will be unable to walk without assistance, and half of them will require long-term domiciliary care [2-4]. Among survivors of a first hip fracture, there is a high incidence (5–20%) of second hip fractures [5, 6]. Half of all the hip fracture patients will never recover to their pre-fracture functional capacity and 25% of these patients reside in a long-term care institution, one year after sustaining a hip fracture [7]. Taking these facts into consideration, it is obvious that all our efforts should go towards preventing first and second hip fractures.

Different strategies to prevent hip fractures and consequent hip fracture surgery have been introduced to achieve a reduction in second hip fracture incidence [8-10]. An alternative approach to prevention could be femoroplasty of the contralateral hip during the surgery of the first hip fracture. Recently the results of cement and elastomer femoroplasty were published [11, 12]. Since femoroplasty with flexible elastomer is more likely to prevent intracapsular hip fractures, prediction of fracture localization of the second hip fracture based on the first hip fracture is necessary. Observations in other studies already indicate symmetry in the two fracture localizations. Although there are a lot of data available on first hip fractures, less is known about patients with a second hip fracture. Especially little is known about symmetry in localization of fractures, symmetry in implants, and patient-specific factors that differ between the first and second hip fracture. The aim of this study was to determine the prevalence of second hip fractures and to establish both the localization of the fracture and the type of the implant. We hypothesized that second, contralateral hip fractures often occur in a similar localization as the first. Ultimately this could lead to establishing preventive measures.

PATIENTS AND METHODS

All patients with a proximal femur fracture, admitted to the Leiden University Medical Centre between 1992 and 2007, were included in this retrospective observational study. Patients were selected from two databases at the Leiden University Medical Centre: the financial administration database since January 1992 up to December 2007, and from 1999 to December 2007 the database of the surgical operative (OPERA) codes of proximal hip fractures from the departments of Orthopedics and Traumatology / General Surgery. The second database was included in the search strategy to double-check the financial administrative database. Selection criteria for the search strategy

in both databases were patients with two or more surgical procedures of the proximal femur with either osteosynthesis or a (hemi) arthroplasty. Second, only patients older than 50 years of age were included as this is the cut-off age used by the WHO for an increased risk for low energy impact fractures. Patients who had a bilateral (both left and right) hip fracture during the 16-year follow-up period were identified. Exclusion criteria were high impact trauma and patients with diseases or medication known to have a negative effect on bone metabolism (i.e. corticosteroids). The study was considered a form of good clinical practice with no extra involvement of patients, thus medical ethics approval was waived. After inclusion the paper hospital charts as well as the hospitals electronic database (Mirador) were used to collect the study variables. All radiographs of the bilateral hip fractures were scored as well. The variables scored were: age, gender, preoperative body weight, trauma mechanism, localization of the fracture at the preoperative radiograph (intracapsular: sub capital, femur neck; extracapsular: trochanteric, subtrochanteric), time between both proximal femur fractures, time between arrival at the hospital and the surgical procedure, preoperative comorbidity classification (American Association of Anesthesiologists [ASA]), type of treatment (i.e. type of implant), blood loss, pre- and postoperative hemoglobin (Hb) and hematocrit (Ht), length of hospital stay for each of the fractures, postoperative complications, and time between death and last hip fracture. Furthermore, osteoporosis medication (vitamin D, calcium and bisphosphonates) was noted at three time periods: before and after the first fracture, and after the second fracture. Finally, the radiographs (AP and lateral hip and pelvis) at the first fracture occurrence were assessed for the degree of osteoporosis (the Singh-index) [13]. The inter-observer variability was tested within two weeks (L.K.). In case of disagreement on the Singh index class, a second observer (R.N.) was consulted. Surgery was performed by several surgeons, both staff surgeons and residents under supervision of the two earlier mentioned specialties. All data were entered in an access database, which was converted to an SPSS database for analysis. Statistical analysis was performed using SPSS version 16.0. Agreement for implant choice, if the localization was the same for both fractures, was calculated using Cohen's kappa statistics. Differences in parametric variables were tested with the t-test. Differences between non-parametric variables like the Singh index and ASA-classification were tested with the Wilcoxon signed rank test.

RESULTS

A total of 1,604 patients had hip surgery between January1992 and December 2007. In this period 150 patients (9.4%) had two or more surgeries of the proximal femur. Of these 150 patients, 118 patients were excluded because of either high impact trauma, failing implants or diseases or medication (i.e. corticosteroids) known to have a negative effect on bone metabolism. Patients who had an arthroplasty for indications other than

a fracture (i.e. osteoarthritis, metastasis) were also excluded. Thus, 64 bilateral fractures in 32 patients (2.0%) could be identified to have a proximal femoral fracture after a low impact trauma. The mean age at the first fracture was 77 years (SD 11.7) and for the second fracture 80 years (SD 11.3) (Table 1).

Table 1. Patients characteristics

Characteristic	Fracture 1	Fracture 2
Age (y)	Mean: 77.2 SD:11.7 Missing: 0	Mean: 79.6 SD: 11.4 Missing: 0
Gender	Men: 5 Women: 27 Missing: 0	
Weight	Mean: 66 SD: 16 Missing: 3 Men - Mean: 67 - SD: 25 - Missing: 0 Women - Mean: 66 - SD: 14 - Missing: 3	Mean: 66 SD: 15 Missing: 5 Men - Mean: 77 - SD: 21 - Missing: 1 Women - Mean: 64 - SD: 14 - Missing: 4
Time between fractures (months)	Mean: 27.5 SD: 28.9 Missing: 0	
Hospital stay (days)	Mean: 20.5 SD: 17.8 Missing: 0	Mean:16.3 SD: 17.0 Missing: 0
Operation time (min)[a]	Mean: 79 SD: 44 Missing: 0	Mean: 93 SD: 42 Missing: 0
Pre-operative ASA	1: 2 2: 24 3: 5 4: 0 Missing: 1	1: 1 2: 20 3: 6 4: 1 Missing: 4
Time between arrival in hospital and operation (h)	Mean: 17 SD: 11 Missing: 2 >24 h: 8 - ASA 1: 1 - ASA 2: 6 - ASA 3: 1 - ASA 4: 0 - ASA unknown: 0	Mean: 14 SD: 9 Missing: 0 >24 h: 5 - ASA 1: 0 - ASA 2: 3 - ASA 3: 1 - ASA 4: 0 ASA unknown: 1

Characteristic	Fracture 1		Fracture 2
Blood loss (ml)	Mean: 342		Mean: 275
	SD: 492		SD: 197
	Missing: 18		Missing: 16
Osteoporosis (Singh index, range 1–6)	Fractured hip 1	Non fractured hip	Fractured hip 2
	1: 6	1: 2	1: 9
	2: 4	2: 3	2: 2
	3: 5	3: 4	3: 7
	4: 3	4: 5	4: 5
	5: 2	5: 4	5: 0
	6: 2	6: 4	6: 1
	Missing: 10	Missing: 10	Missing:8
Osteoporosis medication	Before fracture 1	After fracture 1	After fracture 2
	Yes:2	Yes: 3	Yes: 7
	No: 17	No: 17	No: 13
	Missing: 13	Missing:12	Missing:12
Trauma mechanism	Stumbling: 18		Stumbling: 17
	Staircase:1		Staircase: 0
	Missing:13		Missing: 15
Anaesthetics	General: 10		General: 10
	Spinal: 22		Spinal: 19
	Missing: 0		Missing: 3
Hb pre-operative	Mean: 8.2		Mean: 8.0
	SD: 1.0		SD: 0.9
	Missing: 3		Missing: 7
Hb 1 day post-operative	Mean: 6.3		Mean: 6.4
	SD: 1.1		SD: 1.2
	Missing: 16		Missing: 11
Hb 2 days post-operative	Mean: 6.4		Mean: 6.6
	SD: 0.6		SD: 1.0
	Missing: 15		Missing: 13
Ht pre-operative	Mean: 0.40		Mean: 0.38
	SD: 0.04		SD: 0.04
	Missing: 4		Missing: 10
Ht 1 day post-operative	Mean: 0.30		Mean: 0.32
	SD: 0.05		SD: 0.05
	Missing: 16		Missing: 13
Ht 2 days post-operative	Mean: 0.31		Mean: 0.32
	SD: 0.03		SD: 0.04
	Missing: 16		Missing: 16

SD standard deviation
Hb Hemoglobin Unit = mmol/L; Ht hematocrit Unit = L/L
Weight = in kg Hb = hemoglobin concentration in mmol/l Ht = hematocrit in l/l.
Differences were significant only for gender, time between fractures and osteoporosis.

The mean time between the first and second fracture was 27.5 months (SD 28.9). Of all patients 27 were women, and five were men. Of the 32 patients 13 patients died during the follow-up period, with an average survival of 32 months after the

last hip fracture. The Kaplan-Meier survival curve of the patients after the second hip fracture is shown in Fig. 1.

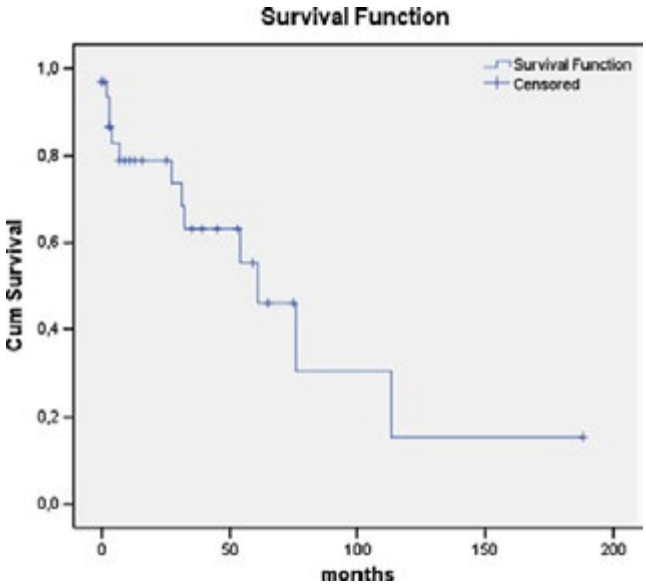

Fig 1. Kaplan-Meier survival curve after second fracture

Of the 64 bilateral fractures 32 were intracapsular, and 32 were extracapsular. The second hip fracture had the same localization as the first at the proximal femur in 24 of the 32 patients (75%) (intracapsular, extracapsular; Table 2). Thirty-one of the 32 intracapsular fractures were femoral neck fractures and one was a sub capital fracture. Six of the extracapsular fractures were subtrochanteric and 26 were trochanteric.

In the group of patients with two intracapsular fractures (Table 3), five out of 12 patients were given the same implant for both fractures. Of all patients with two intracapsular fractures, the first fracture was treated in six of the patients with a DHS, two patients were treated with a cannulated screw, and four with (hemi)arthroplasty. For the second intracapsular fracture two patients were treated with a DHS, two with a cannulated screw and eight with (hemi) arthroplasty.

In the group with two extracapsular fractures at the successive time intervals, the first and second occurring fracture were treated in three (25%) of the 12 patients with the same implant (Table 4). The other differences in implant choice for the first and second intra- and extracapsular fractures are shown in Tables 4 and 5.

The kappa for agreement in implant choice and for localization of fractures was 0.12 for intracapsular fractures and –0.23 for extracapsular fractures. The average hospital stay was 20.5 days (SD 17.8) for the first fracture compared to 16.3 days (SD 17.0) for the second fracture. The mean operation time for the first fracture was 79 min (SD 44), compared to 93 min (SD 42) for the second procedure. The mean weight for

Table 2. Distribution of fracture site per patient at the first and second occurring fracture

Fracture 1	Fracture 2	Intracapsular		Extracapsular		Total
		Subcapital	Femur neck	Trochanter	Subtrochanter	
Intracapsular	Subcapital	0	0	0	0	0
	Femur neck	1	11	4	0	16
Extracapsular	Trochanter	0	3	8	0	11
	subtrochanter	0	1	3	1	5
Total		1	15	15	1	32

Table 3. Choices of implant for intracapsular fractures at the first and second fracture

Fracture 1	Fracture 2			
	DHS	Cannulated screw	(Hemi)arthroplasty	Total
DHS	1	1	4	6
Cannulated screw	0	1	1	2
(Hemi)arthroplasty	1	0	3	4
Total	2	2	8	12

DHS dynamic hipscrew (Synthes Inc)

women declined from 66 kg (SD 14) to 64 (SD 14) (P=0.62) between fractures. In men the opposite was noticed, as men gained weight between the first (mean 68 kg, SD 25) and second fracture (mean 77 kg, SD 21; P=0.30). For both the first and second fracture the preoperative comorbidity (ASA) classification was 2 (range 1–4). The trauma mechanisms involved falls while walking, except for one fall from the first step of a staircase (30 cm height) leading to a first hip fracture. For both the first and second surgeries 10 patients received general anesthesia and 22 had loco regional anesthesia. There was no significant difference in blood parameters between the first and second hip fracture. The mean time between arrival at the hospital and surgery was 17 hours (SD 11) for the first fracture and 14 hours (SD 9) for the second fracture. Eight patients with a first hip fracture had surgery 24 hours or more after arrival at the hospital, compared to 5 patients for the second hip fracture. Osteoporosis medication (Calcium, vitamin D, bisphosphonates) was given to 2 patients before the first fracture, to 3 patients after the first fracture, and to 7 patients after the second fracture. Information about medication was missing from 12 patients. There was a significant difference in Singh index when the first fracture (range 1–6) was compared to the non fractured contralateral hip (range 1–6; P= 0.007), and when the proximal femur at the time of the second hip fracture was compared to itself at the time of first fracture (range 1–6; P=0.008, Wilcoxon test).

The mean number of complications after the first hip fracture was 1.0 compared to 0.8 after the second fracture (Table 5). Six patients had complications in the operation area after a first and 4 patients after a second hip fracture. Nine patients had other, nonoperation wound- related complications after the first hip fracture and 8 after the second fracture.

Table 4. Choices of implant for extracapsular fractures at the first and second fracture

Fracture 1	Fracture 2			
	DHS	Gamma-nail	PFN	Total
DHS	0	1	0	1
Gamma-nail	1	1	4	6
PFN	1	2	2	5
Total	2	4	6	12

DHS dynamic hipscrew (Synthes Inc); PFN proximal femoral nail (Synthes Inc); Gamma nail (Stryker Inc)

Table 5. Complications

Complications	Fracture 1	Fracture 2
Number of complications	Mean: 1.0	Mean: 0.8
	0: 8	0: 10
	1: 6	1: 7
	2: 4	2: 0
	3: 2	3: 3
	Missing: 12	Missing: 12
Complications operation area		
Total	6	4
Wound infections	3	4
Dislocation	2	0
Necrosis	1	0
Pseudo-arthrosis	2	0
Haematoma	1	0
Other complications		
Total	9	8
Delirium	5	6
Decubitus	3	2
Embolus	0	1
Renal/ Bladder complications	3	3

DISCUSSION

During a 16-year follow-up, the prevalence of bilateral proximal femoral fractures in the studied population was relatively low (2%) compared to other studies reporting a second hip fracture in 5–20% [5, 6, 14, 15]. One explanation could be that in our study patients with diseases or medication known to have a negative effect on bone metabolism were excluded. Another and more probable explanation is the variability in patient allocation. Since the Leiden region is a densely populated area with two hospitals with a trauma care unit, it is possible that a patient will be allocated to different hospitals for a first and second hip fracture. Furthermore, patients who were treated for a hip fracture in the LUMC after 2007 were not included in this study. Fractures occurring before 1992 were however noted from the hospital chart.

The survival of the patients in the present study is comparable to other studies [16]. The average time between arrival and operation in this study was short, which reduces mortality [17]. A possible explanation for the fact that patients often have

the same type of fracture in both hips is that fractures have a multi-factorial cause, i.e., not only the bone mineral density and bone structure, but also geometry, play an important role [18].

An interesting finding in this study is the fact that both hips have a different Singh index at the time of the first fracture. The influence of immobilization on the occurrence of osteoporosis after the first hip fracture, as mentioned by some authors [19], will be little, since patients were ambulated the day after surgery. But since the degree of osteoporosis deteriorated further after the first fracture, it might have been prevented with adequate osteoporosis medication. In this study only seven patients of 32 received any form of osteoporosis medication (vitamin D, calcium and bisphosphonates). Also other studies show that osteoporosis is seldom treated after a hip fracture [15, 20]. Treating all patients with osteoporosis after a first hip fracture could prevent 43% of the second hip fractures [21]. In none of the patients a DEXA-scan was made, but according to the Singh index at least half of the patients suffered from osteoporosis at the time of the first fracture, but they did not receive medication afterwards. When operating hip fractures diagnosing osteoporosis is very important. A Singh index on a regular X-ray can give important information about the degree of osteoporosis. Treating osteoporosis should always be considered, as it can prevent further hip fractures. Osteoporotic fractures are known to be preceded by a decline in weight, due to a decline in estrogens in postmenopausal women [22]. In this study the 3 kg difference was not a significant decline in weight for women, probably due to under power of the study. The hospital stay in this study is relatively long. The cause of this is unknown, but a hypothesis is that it is relatively difficult to find places for patients in nursing homes. Another explanation is that a few patients suffered from many complications and for that reason had prolonged hospital admissions, which contributes to a long average stay. An interesting but not significant (P= 0.34) finding in this study is the shorter hospital stay after a second hip fracture. Others suggest that the recovery of patients with a subsequent, contralateral hip fracture is not different from the first hip fracture [23].

Although 24 of 32 patients had a similar localization of the femoral fracture, only eight out of these 24 patients received the same implant in both hips. A factor that has to be mentioned is that Gamma-nails and PFN are implants of the same type, but used by different specialists. If the Gamma-nail and PFN are considered to be a comparable implant, 14 of these 24 patients received the same type of implant. The main reason to choose an implant is the type of fracture [24]. Undisplaced intracapsular fractures should be treated, according to the Dutch guidelines, with internal fixation using a method that is familiar to the surgeon [24].

According to the AO guideline there is no evidence of the superiority of one implant over the other for the fixation of intracapsular fractures. However, patients with a short life expectancy or low mobility demand are considered eligible for hemi-

arthroplasty. The latter is known to have a lower risk of failure than a DHS or cannulated screws in these patients [24]. But also other characteristics of the fracture (bone quality, displacement and comminution) and patients characteristics (age, functional level before the fracture) are important [4]. Internal fixation with screws and nails is associated with less initial operating trauma, but has an increased risk of re-operation compared to hemi-arthroplasty [25]. Also co-morbidity is an important factor in choosing an implant. Parkinson's disease, rheumatoid arthritis or osteoarthritis patients for example require total hip replacement as they have a high risk of postoperative prosthetic dislocation [4]. Probably one of the most important reasons to choose a specific implant is preference and experience of the surgeon. Research showed that treatment choice based on physiological status does not significantly improve clinical decision-making. This study showed clearly that implants were randomly chosen, instead of trying to give the patient symmetrical hips.

CONCLUSION

This small series shows a significant effect of the radiographic osteoporosis appearance as measured with the Singh index on second proximal femur fracture occurrence

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CHAPTER 3

Complications and institutionalization are almost doubled after second hip fracture surgery in the elderly patient

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ABSTRACT

Purpose

To determine patient and hip fracture characteristics, early postoperative complication rate and need for institutionalization at time of discharge from the hospital in patients treated for a second, contralateral hip fracture.

Methods

During a six-year period (2003-2009) seventy-one patients (60 women and 11 men; age range 54 – 94 years) underwent first hip fracture surgery and subsequent contralateral hip fracture surgery at our hospital. Variables including age, gender, American Society of Anesthesiologists Classification (ASA), AO fracture classification, time between both hip fractures, rate and severity of early postoperative complications and destination of discharge were obtained from the electronic medical records. Data from both hospitalization periods were compared.

Results

Forty-six percent of second hip fractures occurred within two years after the first hip fracture. Following first hip fracture surgery 13 patients had one or multiple complications compared to 23 patients after second hip fracture surgery (P= 0.02). The mean time (± SD) between first and second hip fracture in patients without complications after the second injury was 4.3 (± 4.2) years, compared to 2.6 (± 2.1) years in patients with complications after the second injury (P= 0.03). The mean ASA classification of patients without complications after second hip fracture surgery was 2.6 (± 0.6) versus 3.0 (± 0.6) in patients with complications (P= 0.04). After first hip fracture surgery 27 patients (38%) were discharged to an institutional care facility, whereas 72% of patients resided at an institutional care facility after a second hip fracture.

Conclusions

Early complication rate in patients sustaining a second, contralateral hip fracture was almost twice that documented after the first hip fracture. Following second hip fracture surgery, most patients resided in an institutional care facility.

INTRODUCTION

Hip fracture is a public health burden in elderly patients with repercussions that extend beyond the orthopedic injury into the domain of medicine, rehabilitation, psychiatry, social work, and health care economics[1]. There are over 300,000 hip fracture patients in the United States each year. Patients with mental illness, coexisting medical conditions and postoperative complications have a permanent reduction in activities of daily living and require postoperative discharge to an institutional care facility [2, 3]. After hip fracture, mortality risk is increased during the first three months 5 to 8 fold [4]. This excess risk also persists for several years thereafter [5, 6]. Of those who survive the first fracture, up to 16 percent subsequently sustains a fracture on the contralateral side [7, 8]. Assumed risk factors for such second, contralateral fracture include older age [7, 9, 10], weakened motor skills [11], weakened cognitive function [7, 12, 13], respiratory disease [12] and solitary life [14].

In contrast to the extensive documentation of the impact of a first hip fracture, the consequences of a second, contralateral hip fracture on the disability of these frail patients remain largely unknown. Limited data suggest that patients with a second hip fracture might have worse mobility shortly after the surgery compared with patients with a first fracture [15, 16]. In a recent study of 473 patients with a sequential hip fracture, the second injury was associated with greater loss of independent mobility and changes in residential status compared with single fractures at one-year follow-up [17]. However, Sawalha and Parker in their study of 633 patients who sustained a second, contralateral hip fracture, could not corroborate the decreased level of mobility at one-year follow-up [18]. The mortality rate in their cohort, on the other hand, was significantly higher after a second hip fracture at one year than after a first fracture. No data are available on the immediate postoperative outcome of patients after second hip fracture.

The specific aims of this study were to compare (1) patient and fracture characteristics of first and second, contralateral hip fractures, (2) the early postoperative complication rate in both groups, and (3) the need for institutionalization at time of discharge from the hospital of patients after surgery for a second, contralateral hip fracture with those of the same patients after their first hip surgery.

METHODS

Patient selection

The electronic medical records and X-ray images of all patients with hip fractures (ICD-10 code S72.0 or S72.1) operated between 2003 and 2009 in the St. Elisabeth Hospital (Tilburg, The Netherlands) were reviewed to identify patients who were treated for both

a first and second, contralateral hip fracture. Patients under the age of 50 years at the time of injury, second, ipsilateral fractures and fractures following high-energy trauma were excluded from the study. 920 eligible patients underwent hip fracture surgery in the study period. Of these, 71 patients (prevalence 8%), 60 women and 11 men; age range 54 – 94 years, were treated for a second, contralateral hip fracture at our institute and were included in this study.

Data collection

The characteristics and outcome after the first and second fractures in the included patients were obtained from (1) the electronic medical record system and (2) a prospective complication database.

Data were collected prospectively in the electronic medical record system including patient age, gender, medical history, AO classification of the fracture and the appropriate ICD-10 and billing code recorded upon each admission to the emergency department, time of hospital admission, American Society of Anesthesiologists (ASA) classification [19] and time of surgery. Finally, the electronic medical record was reviewed for the complete postoperative course, including in-hospital complications and mortality, date of discharge and destination of discharge.

As for the prospective complication database, the standard definition of a complication as formulated by the Association of Surgeons of The Netherlands was used: 'A complication is any condition or event, unfavorable to the patient's health, causing irreversible damage or requiring a change in therapeutic policy'. Complications were coded prospectively according to the Trauma Registry of the American College of Surgeons Committee on Trauma (TRACS) [20]. In addition, a free-text description of the complication was also recorded. As prospective registration of complications is known to be often incomplete and inconsistent, in this study all patient records were fully reviewed for non-registered complications and all entries were checked. Early post-operative complications were defined as those occurring within 30 days of surgery. Complications were ranked according to the Clavien-Dindo classification based on a therapy-oriented, four-level severity grading (ranging from Grade I – minor risk event not requiring therapy – to Grade IV – death due to a complication) [21]. In-hospital mortality and mortality within 30 days of surgery were scored separately. As this was a retrospective review, no actual patient follow-up visit for the specific purpose of this study took place.

Statistical analysis.

Statistical analysis was done using Statistical Package for the Social Sciences Statistics 18 (SPSS Inc., Chicago, Illinois). To compare complications in the 71 patients after their first and second hip fracture surgery with continuous data and a normal distribution,

a paired Student's t-test was used. For nominal data following hip fracture surgery we used McNemar's test, a non-parametric test. ASA classification during first and second hip fracture surgery was compared using Wilcoxon's test. *P* values less than 0.05 were considered significant.

RESULTS

Patient and fracture characteristics (Table 1 and 2)

The mean time between first and second hip fracture was 3.4 ± 2.9 years (range 0.25 - 12.6 years). Forty-six percent of the second hip fractures occurred within 2 years after the first hip fracture. The percentage of intracapsular hip fractures was 63% for the first fracture and 59% for the second fracture (*P*=0.50). According to AO fracture classification no significant difference between the first and second hip fractures was found. The fracture-types were similar with respect to intra- or extra-capsular location in 52 patients (73%). The mean time from arrival at the hospital to surgery and the duration of hospital stay were similar after first and second hip fracture surgery.

Table 1. Patient and fracture characteristics (n = 71 patients).

	First hip fracture	Second hip fracture	*P* value*
Gender (n (%))			
Female	60 (85%)	*Same patients*	-
Male	11 (15%)	*Same patients*	-
Age (years)			
Mean ± S.D.	80.0 ± 8.1	83.4 ± 7.7	<0.0001
Range	54 – 94	56 – 95	
Mean time between hospital admission and surgery (days)	0.9 ± 1.5	0.8 ± 1.0	0.56
Mean duration of hospitalization (days)	15.7 ± 15.4	13.4 ± 12.0	0.35
Type of fracture (n (%))			0.50§
Intracapsular	45 (63%)	42 (59%)	
Extracapsular	26 (37%)	29 (41%)	

Plus-minus values are means ± SD. *Student's t-test, §McNemar's test

Table 2. American Society of Anesthesiologists (ASA) classification of physical health (n = 71 patients).

	First hip fracture	Second hip fracture	*P* value*
ASA classification (n (%))			**0.001**
1	2 (3)	1 (1)	
2	42 (59)	24 (34)	
3	24 (34)	39 (55)	
4	3 (4)	7 (10)	
Total	71 (100%)	71 (100%)	

* Wilcoxon's test

The ASA classification prior to first hip fracture surgery was 2.4 (± 0.6) versus 2.7 (± 0.7) prior to second hip fracture surgery (*P*= 0.001). The mean ASA classification of patients without complications after second hip fracture surgery was 2.6 (± 0.6) versus 3.0 (± 0.6) in patients with complications (*P*= 0.04).

Postoperative complication rate (Table 3)

Following first hip fracture surgery 13 patients had one or multiple complications compared to 23 patients after second hip fracture surgery (*P*= 0.02). There was one patient with two complications after first hip fracture surgery (a urinary tract infection and wound infection) compared to four patients with two complications after second hip fracture surgery (technical failure and urinary tract infection; cardiac and technical failure; cardiac and deep wound infection; pneumonia and urinary tract infection). Out of the 13 patients with complications after first hip fracture surgery, only 5 had complications after the second fracture. Four of these 5 patients had complications after the second hip fracture surgery that were similar to the complication after first fracture (pulmonary, cardiac and two wound infections).

Six patients with second hip fracture died in the hospital, and one additional patient died within 30 days of the second fracture, thus the mortality within 30 days of surgery of the second hip fracture was 10%. According to the Clavien-Dindo classification, 1 grade III complication occurred after first hip fracture, compared to 7 severe complications, grade III and IV, after second hip fracture. The mean duration between first and second hip fracture in patients without complications after the second injury was 4.3 (± 4.2) years, and 2.6 (± 2.1) years in patients with complications after the second injury (*P*= 0.03).

Table 3. The 30-day postoperative complication rate comparing first hip fracture and second, contralateral hip fracture (n= 71 patients).

	First hip fracture (n=71)	Second hip fracture (n=71)	*P* value§
Complications (n)	14	26	0.02
Patients with complications (n)	13	23	0.02
Type of complication (n)			
Cardiac	4	6	
Pneumonia	1	4	
Wound infection	4	5	
Urinary tract infection	4	2	
Dislocation – technical complication	1	2	
Severe complication leading to death (Type IV)		7	

§ McNemar's test, * 6 patients died during hospitalization, one patient died after discharge within 30 days.

Discharge institutionalization (Figure 1)

After first hip fracture surgery 27 patients (38%) were discharged to an institutional care facility, 44 patients (62%) returned to their original residence. After second hip fracture 24 patients who originally resided home were discharged to an institutional care facility and 23 of the 27 patients who already resided at an institutional care facility returned to the same residence. Eventually, 47 patients (72%) resided at an institutional care facility after the second hip fracture.

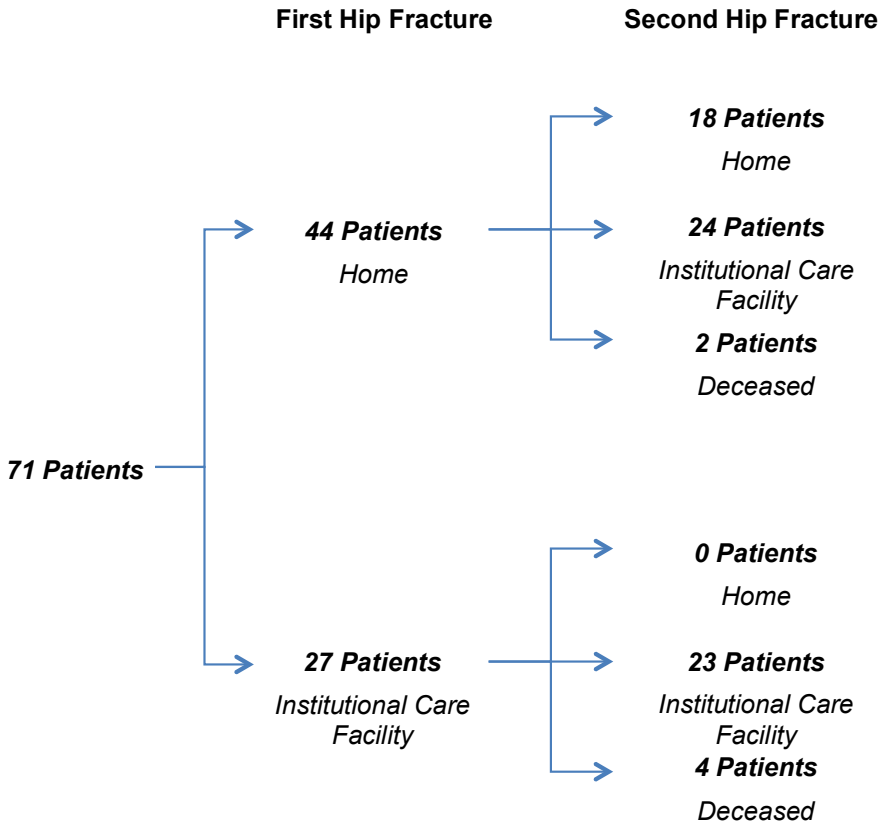

Figure 1. Destination outcome at discharge after first and second hip fracture

DISCUSSION

In the present study, we compared patient and fracture characteristics, early postoperative complication rate, and the need for institutionalization at the time of discharge from the hospital in seventy-one patients treated at our hospital from a consecutive series of 920 first hip fractures. It is well known that a major operation in elderly individuals results in functional decline [22, 23]. It could be postulated that the first hip fracture and its treatment in elderly might result in a persistent reduction

in performance and physiological reserve as well. Such impairment of function in the older surgical patient is consistently identified as a predictor of subsequent poor postoperative outcome and the need for discharge to an institutional care facility [23-25]. Thus an optimal treatment to insure a mobile independent patient is of importance. Other factors for higher complication and mortality risks are advanced age, absence of a partner, dementia, a lower pre-fracture level of ADL independency or mobility problems [25-27]. Also ASA-classification due to diseases affecting generic health might be increased. It is unknown whether a second, contralateral hip fracture is associated with an additional risk of postoperative complications and institutionalization after discharge from hospital. Some use a discharge score at admission in these, often frail, fracture patients, to facilitate an optimal postoperative rehabilitation and expectation course for both patients and their family as well for the treating physicians [28].

We found that the characteristics of our cohort were similar to those reported in the literature so far: the majority of patients with hip fracture were female (85%); almost half of the second, contralateral hip fractures occurred within two years of the first hip fracture; and the anatomical classification of contralateral fractures was identical to the primary fracture in more than two thirds of patients [10, 29, 30] [12, 18] [18, 30, 31]. Approximately 8% of all hip fracture patients in our study sustained a second hip fracture, this is comparable to incidence rates found in the literature [7, 8, 10]. It could be possible that patients were brought to another institution for their second hip fracture. If so, the 8% could be an underestimate of the true incidence of second hip fractures. However, our hospital has a regional trauma function, therefore patients would have to relocate outside our region to be admitted to another hospital for their second fracture.

The 30-day mortality rate after second hip fracture in our study is comparable to previously determined mortality rate from a single hip fracture at our institute. In this previous study published in 2010 the hospital mortality of a similar cohort of patients operated for a single pertrochanteric femoral fracture in our hospital was 11% [32].

In our study, significantly more patients had postoperative complications after the second hip fracture than after the first hip fracture, with close to twice the number of complications per patient after second hip fracture surgery (table 3). In addition, complications were more severe, according to the Clavien-Dindo classification, after second hip fracture compared to those documented after first hip fracture. One explanation for this increased complication rate might be that patients were inevitably older at the time of the repeat injury and were hence more susceptible to medical complications. In our study, patients were on average 3.4 years older at the time of second hip fracture. Older age has been linked to increased mortality rate after second hip fractures [7, 10, 18, 25, 33]. The question raises whether age itself is an independent risk factor for postoperative complications, eventually resulting in death, or that more chronic comorbidity and reduced physiological reserves are the true independent risk

factors. This last argument is supported by a significantly higher ASA-classification in patients with complications after a second fracture. However, the question whether age or ASA-classification contribute to a worse outcome after a second fracture, cannot be answered from the current data. In addition, no rigid method such as the Charlson Comorbidity Index which classifies comorbid conditions that might alter the risk of mortality has been used in the present study [34]. A logistic regression that corrects for all potential independent risk factors and confounders would be required, but is unreliable using the current data set. Although this is a limitation of our study, the mean age of patients with postoperative complications after second hip injury did not differ significantly from those without postoperative complications (83.3 ± 7.1 years versus 83.6 ± 8.1 years, respectively). More importantly, the time interval between both hip fractures was shorter in patients with postoperative complications after second hip fracture as compared to those without. It has been shown that fewer than half of ageing patients recover to their pre-illness levels of functioning one year following hospitalization for acute illness [35-37]. Therefore, the finding that those patients who required a second intervention sooner had more complications suggests that these patients were likely in a state of lingering reduced physiologic reserve after the first fracture, as suggested by the higher ASA classification in these patients. Such accumulated frailty in geriatric patients has been associated with increased susceptibility to postoperative complications and the need for institutionalization after discharge [24].

Another limitation of the present study is that reliable information on pharmacy usage was not available at the time of hospital admission. This is due to the retrospective nature of our study; therefore we performed no analysis of this presence of drugs-at-admission effect on complications. Patients who are admitted with a second hip fracture often use five or more drugs daily [38]. Polypharmacy, combined with repeat immobility [39], indwelling devices such as urinary catheters [40] and a nutritional status that deteriorates during hospitalization [41] have been shown to put frail older patients at risk of hospitalization-associated disability with resultant loss of ability to live independently [37]. This phenomenon is supported by the observation in our study that only approximately one third of the patients was able to return to their own home after treatment for second hip fracture.

The finding that postoperative complications and institutionalization after discharge from the hospital are increased in patients sustaining a second, contralateral hip fracture has implications for clinical care. Patients that are admitted with a second hip fracture, especially those with a relatively short period between the two hip fractures, might be good candidates for targeted interventions such as acute care of elders units (ACE) or geriatric evaluation and management (GEM) units. In such units a multidisciplinary team takes primary role in patient care to reduce the incidence of complications. Such units have been shown to increase the likelihood of functional

improvement by the time of discharge and lower the need for nursing home care [42]. The integration of individual consulting services such as physical therapy, occupational therapy and geriatrics into a multidisciplinary team has been particularly promising following hip fracture [37].

Given the detrimental impact of second hip fracture on elderly patients, secondary fracture prevention efforts are clinically justified. Randomized trials have shown that available osteoporosis therapies are effective in preventing secondary fractures [43, 44]. However, a considerable amount of patients who have sustained one hip fracture do not receive adequate pharmaceutical treatment for osteoporosis [45]. Poor compliance with oral bisphosphonate therapy and the short time between first and second fracture have been shown to diminish the efficacy of this treatment for secondary fracture reduction [46]. Therefore, in frail patients at particular risk of second, contralateral hip fracture (i.e. older age with weakened motor skills, visual impairment, dementia, respiratory disease, or solitary life after first hip fracture) alternative medical approaches such as an external mechanical protection with hip protectors might be considered [47] as well as balance training for patients [48]. A surgical option, although still in the experimental phase, is internal stabilization with bone cement or elastomer through femoroplasty of the contralateral hip during surgery of the first hip fracture is promising because of its instant protection potential and inherent compliance [49, 50].

In conclusion, the need for discharge institutionalization was increased and the early postoperative complications were almost doubled in patients sustaining a second, contralateral hip fracture compared to the first hip fracture. Prevention of these second hip fractures is urgently needed.

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PART II

Elastomer Femoroplasty

CHAPTER 4

The concept of preventive elastomer femoroplasty in individuals with high risk of hip fracture

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INTRODUCTION

The increasing number of osteoporotic hip fractures in the expanding elderly population and its burden on healthcare resources call for urgent preventive action. Among numerous preventive therapies only bisphosphonates have proven to be effective in preventing osteoporotic fractures in large randomized trails [1, 2]. However discussion remains on the optimal duration of therapy. Furthermore, up to three quarters of patients are not compliant in using their osteoporosis medication, possibly due to the side effects of the medication [3]. This might be an explanation for the high incidence of second, contralateral hip fractures. Also, the late start of bisphosphonate therapy after the initial fracture could be a contributing factor since a considerable number of second hip fractures occur in the first 2-3 years after the first hip fracture, when the effect of the bisphosphonate on bone strength has not yet set in [4].

A different, preventive measure is a wearable orthosis, the Hip-protector. This protective underwear is either of the "crash helmet type" with a Carbon-fiber or nylon shell, covering the greater trochanter of the hip, or of the "energy-absorbing type" with a soft cushion made of materials like silicone or D3O®. Both of these systems aim to reduce the focused force beneath an estimated fracture threshold. When wearing a hip-protector an immediate effect on the incidence of hip fractures has been shown [5]. However they require patient compliance and are therefore an ineffective intervention in those living at home [6, 7].

Contrary to these previously proposed preventive measures, elastomer femoroplasty (EF) does not require patient compliance and will have an immediate preventive effect. This new approach does not aim to prevent the hip fracture itself, but aims to prevent dislocation after the fracture, thus enabling bone healing with fracture consolidation conservatively, without surgery. This conservative treatment is comparable to that used for non-dislocated fractures [8, 9].

The efficacy of this preventive EF will be optimal in those patients with a high risk of femur fracture. After ipsilateral hip fracture surgery with either osteosynthesis or hemiarthroplasty patients have an increased risk of acquiring a contralateral hip fracture of up to 16 percent [10-12]. Other factors that increase the risk of hip fracture include: older age [10, 12, 13], weakened motor skills [14], dementia [10, 15, 16], respiratory disease [15], solitary life [17] and radiographic osteoporosis at the hip (the Singh Index) [18]. Treating the contralateral hip of high-risk patients during ipsilateral hip fracture surgery might optimize the efficacy of preventive EF. The technique of preventive EF and its potential use in these high-risk patients will be discussed.

METHODS AND MATERIALS

Operative technique

A schematic overview of the preventive strategy of EF is displayed in Figure 1. After ipsilateral hip fracture surgery with either osteosynthesis or hemiarthroplasty the contralateral hip is preventively treated with EF during the same operative session.

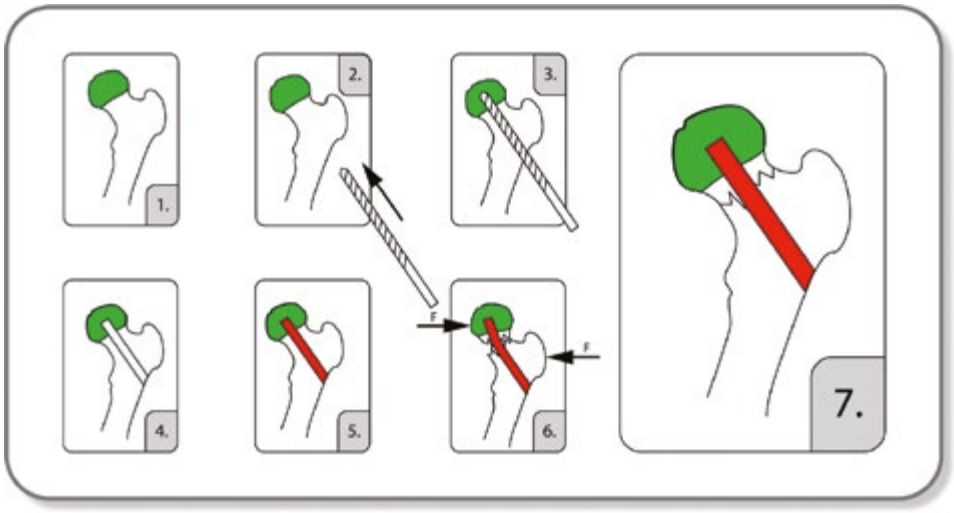

Fig 1. Schematic overview of the principal of preventive elastomer femoroplasty (EF). 1) Intact proximal femur. 2) 3.5 cm hole is drilled in the lateral cortex. 3) Eccentric drill creates cavity in the proximal femur en femur head. 4) Cavity in the proximal femur. 5) Cavity filled with elastomer. 6) Forces on proximal femur during impact and fracture. 7) Situation after fracture, the elastomer prevents fracture dislocation.

The intervention starts with sterile draping of a small area below the greater trochanter of the contralateral hip. A stab incision is made in the skin and blunt dissection towards the lateral cortex of proximal femur is achieved. Using fluoroscopy, a Kirschner-wire is positioned through the center of femur neck and head, not through the femur head. Over the wire a 3.5 mm hole is drilled. Through this 3.5 mm hole in the lateral cortex an excentric drill is used to drill a 10mm channel in the femur neck and a 15 mm anchor in the femur head (Fig. 2). Through a 7-gauge trocar the channel is filled with the elastomer, starting proximally and retracting while filling the cavity. The stab incision is closed using a steristrip.

The Elastomer

The elastomeric compound that was used in our experiments is a polydimethylsiloxane (PDMS). For femoroplasty the material needed specific chemical and mechanical

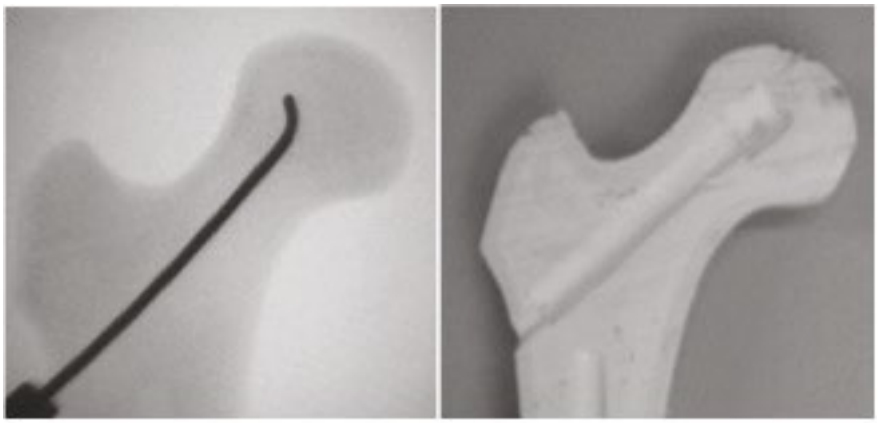

Fig 2. The principle of using an eccentric drill used to create a cavity in the proximal femur of a Sawbone.

properties: the material had to be non-toxic and cross-link isothermally in the presence of blood, without the release of toxic by-products. It should be injectable through a large bore needle, therefore the viscosity in the non-cross-linked form had to be low. The curing-time should be sufficiently long (5–10 min) to be able to complete the injection-process before the material becomes too viscous. When cured, it should be non-thrombogenic and the strength and durability had to be sufficient to withstand stresses during cyclic loading and unloading. Silicone-based elastomers meet the above requirements of blood compatibility and mechanical properties, furthermore they have been successfully used in vivo [19, 20].

The Silicone-based elastomer was developed by the Technical University of Delft, the Netherlands (Prof. van Turnhout MSc PhD, van den Berg MSc PhD and Alili MSc) [21]. The formulation consists of a two-component room temperature addition-cure liquid silicone formulation, obtained from Viazym BV [ViaZym BV; Delft, the Netherlands]. These two components are:

- A platinum containing Vinyl terminated polydimethylsiloxane (PDMS) with an optimized molecular weight with regard to viscosity versus mechanical properties of the cured end-product (elongation to break, modulus). This component further contains surface-treated amorphous silica and a sesqui-siloxane-like material called Vinyl Q, which is known to increase shear-strength of the final cured elastomer without an evident increase in viscosity.
- A methylhydro-dimethyl-siloxane copolymer containing vinyl terminated poly- dimethylsiloxane (PDMS). This component further contains surface-treated amorphous silica and Vinyl Q. The substance has an average polymerization time of approximately 5 minutes.

DISCUSSION

We propose a new and experimental preventive percutaneous approach to reduce the incidence of second, contralateral hip fracture surgery in high-risk patients. Careful analysis of biocompatibility and a phased introduction, like proposed for all new implants should be performed to have an optimal patient safety [22]. After this a cost-effectiveness analysis is mandatory before any preventive measure is installed.

Applying EF in the contralateral proximal femur immediate after ipsilateral hip fracture surgery is likely to take some extra surgical time and although minimal invasive, will cause some extra surgical trauma to the patient. Furthermore filling the proximal femur could cause the release of fat emboli in vivo, comparable to those occurring during cementation of a hip stem (i.e. hip arthroplasty). Future studies will have to focus on the effect of these extra surgical risks on morbidity and mortality. These results will then have to be compared to the increased morbidity and mortality after surgery of second, contralateral hip fracture surgery.

Considering that the likelihood of acquiring a second, contralateral hip fracture is high and health care costs of treating a second hip fracture are at leased 20 times higher than the expected cost of EF, this preventive measure could well be cost-effective. Patient selection based on factors that increase the risk of a second, contralateral hip fracture, such as high age, high Singh index on radiographic image and dementia [10, 12, 15, 16, 18] will improve both clinical outcome as well as cost effectiveness of EF.

In vitro experiments on fracture load after EF have been done and show promising results [23, 24]. Additionally we have tested the dislocation loads after a fracture was created in an EF treated femur during cyclic loading and unloading [25]. We found dislocation loads that were considerably higher than the loads on the proximal femur during normal gait, suggesting that the patient can walk unrestrained on a fractured EF treated hip. Future in vivo experiments, for instance using roentgen stereophotogrammetric analysis (RSA) [22, 26, 27], will have to confirm our in vitro observations.

In conclusion, EF is a new and experimental approach, which might have an impact in reducing the burden of second hip fractures on patient quality of life and at the same time have a positive effect on the use of our health care recourses. EF could well be a cost effective preventive strategy since the incidence of second hip fractures is high and the additional costs of contralateral EF during ipsilateral hip fracture surgery is expected to be low. In vitro results of EF with respect to both biocompatibility as well as mechanical properties look promising, future clinical trials are needed to prove its efficacy in patients.

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CHAPTER 5

Augmentation with silicone stabilizes proximal femur fractures: an in vitro biomechanical study

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Clinical Biomechanics March 2009

ABSTRACT

Background

Prevention of hip fracture surgery in the elderly imposes great benefit for patient care as well as for society. The incidence of contralateral, second hip fractures after hip fracture surgery is as high as 20%. Augmentation of the contralateral proximal femur with silicone femoroplasty during hip fracture surgery of the ipsilateral hip could be a new preventive strategy. This study compared the degree of dislocation after a controlled induced fracture between treated and control cadaver femurs.

Methods

Ten paired cadaver femurs were randomly assigned for silicone femoroplasty and biomechanically tested for fracture load and dislocation against their native contralateral control. A load-testing machine was used for fracture induction. All femurs were first fractured in a simulated fall configuration followed by dislocation in a "single leg stance" configuration. Dislocation was accessed using the AO-classification and measuring the Caput-Collum-Diaphysis angle.

Findings

Fracture loads were approximately 10% lower in the treated group ($P = 0.304$). Forces needed to dislocate the proximal femur fractures did not significantly differ in both groups nor did the fracture type and AO-classification. All treated femurs showed complete reposition according to Caput-Collum-Diaphysis angle after dislocation versus only two of the controls ($P < 0.001$).

Interpretation

From the results of this study we conclude silicone femoroplasty stabilizes the proximal femur by restoring hip geometry according to the Caput-Collum-Diaphysis angle after fracture. Future improvements in minimal invasive excavation and injection could make silicone femoroplasty an attractive alternative strategy in the prevention of hip fracture surgery in the growing population of low-demand, elderly patients.

INTRODUCTION

Different strategies to prevent hip fractures and consequent hip fracture surgery have been introduced in the past decades [1-6]. However, these preventive measures have not yet led to a reduction in sequential or second hip fracture incidence [7].People sustaining one hip fracture are 5-9 times more likely to fracture their contralateral hip compared to age matched controls [8]. The 1-year risk of a subsequent fracture can be as high as 10% [9]. The lifetime risk of a second hip fracture has been estimated at 20% but may be as high as 55% [10]. Prevention of osteoporosis should ideally begin in childhood in order to minimize bone loss during life [11]. Treatment of osteoporosis after hip fracture is probably too late to prevent second hip fractures in the first 2 years, whereas preventive augmentation of the contralateral hip during ipsilateral hip fracture surgery could be an instantly available modality to reduce the incidence of second hip fractures.

Recently the results of femoroplasty-cement augmentation of the proximal femur as a means of fracture prevention have been published [12, 13]. The authors showed that cement augmentation increased the strength of cadaver femurs, but it has had no clinical use so far since temperatures associated with curing of cement are high, possibly causing osteonecrosis. Acquiring femoral shaft fractures or even acetabular fractures due to the increased strength of the proximal femur might be another contra-indication for using cement augmentation [12, 13]. To overcome these disadvantages of cement augmentation we devised a method of intra-medullar femoroplasty of the proximal femur with an injectable silicon rubber. Our hypothesis was that silicone femoroplasty restores the geometry of the proximal femur after fracture. The goals of the present study were to evaluate (i) the amount of dislocation according to the Caput-Collum-Diaphysis angle after fracture and after loading in a single leg stance configuration, (ii) the fracture load of augmented femurs compared to the controls and (iii) the load until dislocation after fracture of augmented and control femurs.

METHODS

Ten pairs of osteopenic (6) or osteoporotic (4) human cadaveric femurs from donors with a mean age of 81 years (SD of 7.6 years) were used. Five donors were male and five donors were female. All cadaver femurs were obtained from the Department of Anatomy, Leiden University Medical Centre. Fixation and preservation of all cadavers was performed by injection of embalming fluid into the femoral artery, consisting of 36% formaldehyde with a mixture of ethanol, glycerine, phenol, K_2S0_4, Na_2S0_4, $NaHC0_3$, $NaN0_3$ and $NaS0_3$.

To exclude the presence of focal bone pathology, plain X-ray's were made of all specimens. The femoral Caput-Collum-Diaphysis angle, the so-called CCD-angle, was

measured from the plain anterior-posterior radiograph of each femur using IQ-view® web-viewer (V2.1.0, Image Information Systems Ltd., London). We calculated the degree of osteoporosis of each proximal femur using dual-energy X-ray absorptiometry (DXA) with a Discovery A, QRD scanner (Hologic Inc., Bedford, USA). All femurs were scanned in air. Osteopenia and osteoporosis were defined according to the WHO, using I-scores of, respectively, <-1 standard deviation and <-2.5 standard deviation from the young adult mean value (Report WHO Study Group, 1994).

From each pair, one femur was randomly selected for femoroplasty; the contralateral femur of the same donor was used as a control. We used a regular electric drill to drill a 10 mm hole in the femur assigned for femoroplasty. This channel was located centrally in the femoral neck reaching into the femoral head approximately 4-5 mm short of the medial femoral head cortex. To achieve a reproducible hole all femurs were drilled using fluoroscopy with a mobile X-ray machine (Pulsera® Mobile C-arms, Philips Heathcare, Eindhoven, The Netherlands). After drilling this 10 mm hole we used a specially constructed eccentric drill bit to excavate the femoral head to a diameter of 14 mm. The drilled cavity was cleaned by pulsed lavage system (Interpulse Stryker®, Kalamazoo, USA).

Plain anterior-posterior and lateral radiographs and DXA-scans were made after drilling. Polydimethylsiloxane (PDMS, Via-Zym BV, Delft, The Netherlands) was injected into the proximal femur using a 50 cc syringe. PDMS is a silicone rubber composed of two components. It is widely used *in vivo* because of its physiological inert properties [14]. PDMS initially has a low viscosity, it cures without exothermic heat, there is no release or formation of by-products as it hardens (polymerization and cross linking) in a watery environment at 37° C [15]. The injected volume needed to fill each femur was registered. All femurs were placed with the femoral head pointing down to prevent the silicon from running out while curing. Although the curing time of our silicone is approximately 15 min at room temperature all femurs were left to rest for 24 h. During curing and in between examinations and tests the femurs were kept moist with cloths drenched in formaldehyde mixture. Plain radiographs were made to record the distribution of silicone.

Augmented and control femurs were biomechanically tested using a LR5 *KPlus* 5 kN load testing machine with a XLC-50 K-Al load cell and NEXYGENP/us material test and data analysis software (Lloyd Instruments, Fareham Hants, UK) with a data acquisition rate of 8 kHz. All femurs were fractured by simulating a fall on the greater trochanter in a modified Hayes-fall configuration [16]. The femoral shaft was firmly held by a steel arm in a 20° angle from the horizontal plane and with the femur head 15° internally rotated (Fig. 1a). The load was applied using a silicone-coated cup attached to the crosshead of the testing machine. The crosshead moved with 2 mm/s and stopped automatically when the load cell registered an abrupt reduction in load of 50%. The recorded load was defined as fracture load. After each specimen was fractured, plain

anterior-posterior and lateral radiographs were made to determine the fracture type, AO-classification and to calculate the CCD-angle.

After a femoral fracture had occurred, each specimen was placed in the testing machine in a vertical position using a "single leg stance" configuration [17]. This fixture holds the femur in an upright position 20° from the vertical in the coronal plane with 15° endorotation (Fig. 1b). The actuator moved with a speed of 1 mm/s and stopped when an abrupt reduction in load of 50% was detected. The recorded load was defined as dislocation load. After the drop in force the crosshead returned to its original position allowing spontaneous or silicone-induced reposition. Again plain anterior-posterior and lateral radiographs were made to determine the fracture type (subcapital, transcervical and trochanteric), AO-classification and to calculate the CCD-angle. From these data we determined the amount of dislocation between the initial fracture and the increase of dislocation at the fracture site after loading in the single leg stance configuration, based on the increase in CCD-angle and fracture classification.

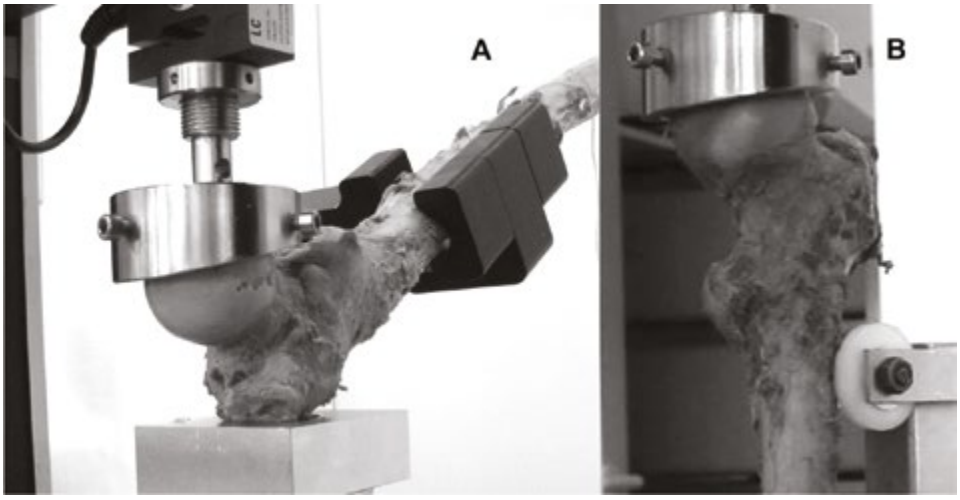

Figure 1. A: Simulation of fall on greater trochanter, the femur is fixed with 15° endorotation and 20° angle with the horizontal plane. B: Single leg stance configuration, the femur is fixed upright, with a 20° angle from the vertical plane and 15° endorotation.

Statistical analysis of the data was done using SPSS. Student-1 tests were performed to determine significance in fracture load, load until dislocation and CCD-angles, calculating *P*-values and 95% confidence intervals. *P*-values of <0.05 were accepted as significant. Correlation between fracture load and DXA results was determined by calculating the Pearsons (r) correlation.

RESULTS

All femurs were paired and randomly assigned to either SF or control. Therefore both groups were similar with respect to age and bone mineral density (BMD). Characteristics of the cadaveric femurs are displayed in Table 1. We used osteoporotic or osteopenic specimens with an average I-score of -2.14 (range: -1.3 to -3.5) and BMD 0.702 g/cm^2 (range: 0.519-0.839). DXA-scans made after drilling the channel for femoroplasty showed no significant decrease in bone mineral density (BMD 0.695 g/cm^2 (range: 0.515-0.836), T-score -2.2 (range: -1.3 to -3.5)).

Table 1. Baseline characteristics of cadaver femurs in both groups, BMD: Bone Mineral Density, T-score: score used to express BMD in standard deviation from the mean BMD of a young adult, CCD-angle: Caput-Collum-Diafyse angle.

	Control Mean (SD)	**Silicone femoroplasty** Mean (SD)
BMD	0.703 g/cm^2 (±0.111)	0.702 g/cm^2 (±0.120)
T-score	-2.14 SD (±0.74)	-2.14 SD (±0.81)
CCD-angle	129° (±3)	128° (±4)

During silicone injection there was no leakage of silicone through vascular penetrations in the proximal femur. The mean volume of PDMS per femur was 35 cc (range: 28-42 cc). The X-rays after filling showed a regular and reproducible pattern of silicone distribution in the head, neck and trochanteric regions of the proximal femur (Fig. 2).

Fracture and dislocation loads for each femur in both control and SF group are displayed in Table 2. The mean fracture load in the simulated fall configuration was 3097 N for the control group versus 2795 N for the SF group (P= 0.304, 95% CI of the difference: -929 to 325). There was a linear correlation between BMD and fracture load in both groups. The correlation coefficient for SF group r = 0.86 and for the controls r = 0.60. Forces needed to dislocate fractures (dislocation load) in a single leg stance configuration were 1436 N in the control group versus 1574 N in the SF group (P= 0.573, 95% CI: -394 to 668). The stiffness during dislocation was 101 N/mm in the control group versus 119 N/mm in the SF group (P= 0.260, 95% CI: -16 to 53) with a maximum displacement of, respectively, 15 mm and 14 mm (P= 0.458, 95% CI: -2.8 to 1.4).

The CCD-angles measured before and after fracture and after dislocation are displayed in Fig. 3. Before fracture there were two outlying observations in CCD-angle in the control group, 123° and 125°, respectively. These outliers were approximately within 2-3.5 interquartile ranges from the median of the observations and were accepted as normal variations in anatomy. In the control group the CCD-angels were 129° (range: 124-133) after fracture and 113° (range: 93-140) after loading until dislocation. In the SF group the CCD-angles after fracture and after loading until dislocation were, respectively, 130° (range: 123-134) and 128° (range: 121-133). In the control group only

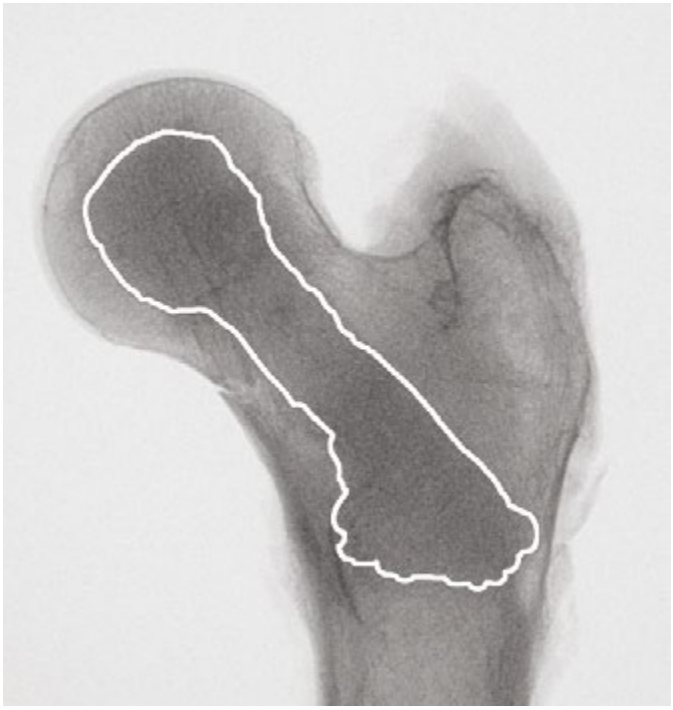

Figure 2. X-ray image of a Silicone augmented proximal femur. The line marks the deposition of the Silicone.

two femurs had either spontaneous reposition of the fracture elements or a minor dislocation without alteration of the CCD-angle. Whereas all 10 SF augmented femurs maintained pre-fracture geometry according to CCD-angle. In the control group the absolute differences in CCD-angle (ACCD) were 2° (range: 0-7) after fracture and 20° (range: 3-39) after dislocation. In the SF group the ACCD after fracture was 2° (range: 0-4) and 1° (range: 0-4) after dislocation (*P*= 0.001, 95% CI: -27 to -10).

There was a large variability in the distribution of subcapital, transcervical and trochanteric fractures in both groups. In the control group there was one subcapital fracture, seven transcervical fractures and two trochanteric fractures. In the SF group there was one subcapital fracture, five transcervical fractures and four trochanteric fractures. In the SF group three trochanteric fractures ran through the drill hole in the lateral cortex. These three fractures were stable after load bearing and no significant dislocation occurred.

AO-classification of the fractures in the control group showed a predominance of B2 (7) fractures, one B3 fracture and two Al fractures. In the SF group there were four B2 fractures, one Bl fracture, three Al fractures and two A3 fractures.

Table 2: Forces needed to break and dislocate the Silicone augmented and control femurs

	Load until break (N) *simulated fall configuration*		**Load until dislocation (N)** *"single leg stance" configuration*	
Femur pair #	***Control***	***SF***	***Control***	***SF***
#1	1920	3696	861	967
#2	2904	2052	2326	912
#3	1407	1372	878	913
#4	2767	2410	600	665
#5	3210	3299	1067	2279
#6	3136	3340	2492	2875
#7	2872	2009	1299	1215
#8	4649	3484	1285	806
#9	4710	3910	1832	2807
#10	3398	2381	1723	2297
Mean (SD)	**3097(1030)**	**2795(856)**	**1436(638)**	**1574(883)**

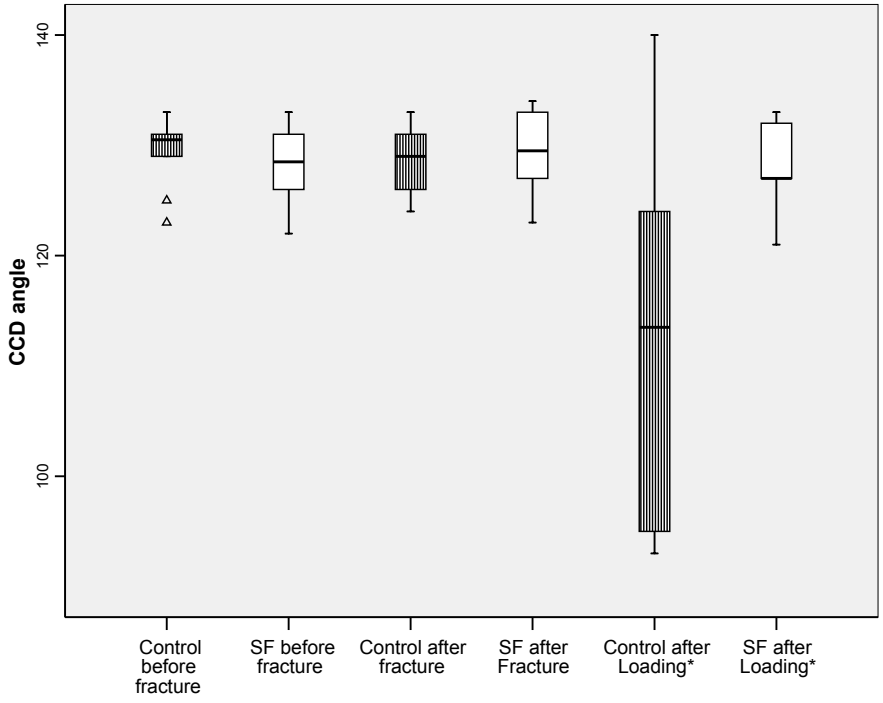

Figure 3. The measured CCD-angle of the SF group compared to the control group before fracture, after fracture and after loading*
(* loading in a "single leg stance" configuration until dislocation)

DISCUSSION

Augmentation of the proximal femur could be a new preventive strategy to the increasing demand on healthcare resources of hip fractures and consequent hip fracture surgery. We tested a method of internal augmentation that does not necessarily increase the proximal femur strength but restores the geometry of the proximal femur in case of a fracture. Increasing the strength of the proximal femur to prevent future fractures by augmentation or enhancement with injectable cement (Femoroplasty) has also been proposed [12, 13]. However in case of a fall the energy is passed on to parts of the hip without augmentation, like the femur shaft or acetabulum. A fracture in those regions often requires more extensive surgery with subsequent increased morbidity and mortality [18-20]. The aim of augmentation with silicone is not prevention of fracture but prevention of fracture dislocation. We showed that SF restores proximal femur geometry according to CCD-angle after fracture. In our study the fracture load is not increased compared to the controls and fractures in the SF augmented hip therefore showed a similar distribution of subcapital, transcervical and trochanteric fractures compared to the control group. We did not observe femoral shaft fractures in our experiments.

The results from the DXA-scans show that in our experiments the drilling of a hole and excavation of the proximal femur has no significant negative effect on measured BMD. However the average load needed to fracture the proximal femur in the SF group was approximately 10% lower than the fracture load in the control group. Although this difference was not statistically significant, the large standard deviation in fracture loads limits the statistical power of our study.

The clinical implications of a 10% difference in fracture load are not well established because the risk of fracture is not based on proximal femur strength alone. However these results should be interpreted very carefully. Geometrically restored proximal femurs after a fracture are worse than no fracture at all. Risk of fracture versus benefit of restored geometry should be tested in a cost-benefit or Markov analysis. Furthermore careful selection of patients with the highest risk of falling and consequent contralateral fracture should be made. Finally, refinement of the technique towards minimal invasive introduction of PDMS could possibly overcome the reduction in proximal femur strength. Since the difference in fracture load between augmented and control femurs could well be contributed to the size of the entrance hole in the lateral cortex. Previous studies have in fact shown that the risk of pathological fracture of a femoral metastasis is increased with a cortical bone lesion size of >25-30mm [21-23]. Although the size of our entrance in the lateral cortex was only 10 mm, it is still a considerable gap especially in the smaller femurs. This is confirmed by Kukla et al. who showed a decrease in failure force by 21% after removal of dynamic hip screw and 41% after removal of standard gamma-nail implant in a biomechanical cadaveric study [24]. The entrance hole in the lateral cortex can also explain the increase in trochanteric

fractures in our treatment group. In three of the SF augmented femurs the fracture line passed the entrance hole in the lateral cortex.

We used fixed specimens in this experiment. We justified this second choice material because our primary outcome was reduction of dislocation after fracturing and loading the proximal femur and not load of force. Furthermore each femur was tested to its native, fixed control. However it is still a limitation of our study since most biomechanical experiments are done with fresh frozen cadaveric bones.

No residual dislocation of the hip fractures was observed in our SF augmented group after a mean load of approximately 1500 N was imposed on the fractured femurs. In the control group however, only two femurs showed no significant residual dislocation (i.e. unchanged CCD-angles). These two controls had impacted subcapital fractures and were therefore stable enough to bear this load. The remaining eight fractured hips in the control group dislocated considerably (i.e. change in CCD-angle >13°).

Induced fracture dislocation defined by a sudden drop in load of force was seen in both groups at an average of approximately 1500 N. Hip contact forces with walking in a normal gait pattern are 2-3 times the body weight, ranging from 1500 to 2250 N in an 75 kg individual [25, 26]. This may exceed our dislocation load of 1500 N. However there are arguments to suggest that this is not a major problem. First of all we tested these cadaveric femurs without the influence of the hip joint capsule or musculature. These soft-tissues will considerably contribute to the stability of the silicone augmented femur fracture, as has been shown for non-stabilized fractures [27, 28]. Therefore the force needed to dislocate these fractures could be higher were we to test it with soft tissue. Secondly, after hip fracture or hip fracture surgery patients start to mobilize using walking aids and thus only loading with a smaller portion of their body weight. Pain after a hip fracture of an augmented hip will probably also restrict the patient from full weight bearing. This would reduce the load of force and therefore reduce the dislocation of the fracture elements possibly allowing impaction and consolidation.

PDMS is not a particularly stiff material like steel or regular cement. In fact our load displacement results show an average of 119 N/mm in the SF group. Continuous loading and unloading could cause movement in the fracture leading to complications like delayed or malunion of the fracture due to continuous movement in the SF augmented hip. In such cases or in the case of secondary dislocation, osteosynthesis by for example implantation of a dynamic hip screw or gamma-nail should not be a problem. Normal drills and instruments can easily penetrate the silicone augmented hip which is a major advantage over cement.

In conclusion we showed that silicone femoroplasty stabilizes the proximal femur by restoring hip geometry according to the CCD-angle after fracture. We also found that silicone femoroplasty using a 10 mm hole in the lateral femur cortex is likely to reduce the strength of an otherwise intact bone by approximately 10% and therefore

could increase the risk of fracture in the treated population. Future experiments should clarify whether new minimal invasive silicon augmentation techniques can increase proximal femur strength.

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CHAPTER 6

Elastomer femoroplasty prevents hip fracture displacement. An in vitro biomechanical study comparing two minimal invasive femoroplasty techniques

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ABSTRACT

The purpose of this study was to test femur strength and the ability to prevent fracture displacement of two minimal invasive elastomer femoroplasty techniques.

Methods

A total of sixteen fixed human cadaveric femur pairs were used. From each pair one femur was randomly assigned for elastomer femoroplasty. In these femurs we drilled a 3.5 mm entrance in the lateral cortex. Cavities for the elastomer were created by: group A, balloon and group B an excentric drill. All femurs were fractured by simulating a fall on the greater trochanter. Neck-Shaft-Angles on plain anterior posterior radiographs were measured to determine fracture displacement.

Findings

There was no significant difference in fracture load between controls and treated femurs for group A, 2904 N (SD 1091) versus 2803 N (SD 627) and group B, 2773 N (SD 747) versus 2597 N (SD 834). In group A the mean displacement was 35° (SD 14) for the control femurs and 3° (SD 2) for the treated femurs ($P < 0.001$). In group B the mean displacement was 38° (SD 10) for the controls and 8° (SD 13) for the treated femurs ($P < 0.001$).

Interpretation

The results of this study show that minimal invasive elastomer femoroplasty prevents fracture displacement of the proximal femur. We found no significant compromise in load-to-fracture after minimal invasive balloon or excentric drill femoroplasty.

INTRODUCTION

Hip fracture and consequent hip fracture surgery is associated with increased morbidity, functional decline, and death, as well as increased use of health care services [1]. Different strategies to prevent hip fractures have been introduced in the last three decades. These preventive measures have however not yet led to a reduction in second hip fracture incidence [2-8]. The one-year risk of a second hip fracture is still as high as 10% [9]. The lifetime risk of a second hip fracture has been estimated at 20% but may be as high as 55% and people sustaining one hip fracture are 5-9 times more likely to fracture their contralateral hip compared to age matched controls [10, 11]. Treatment of osteoporosis after hip fracture is probably too late to prevent second hip fractures in the first 2 years. Ideally people at risk of osteoporotic fractures should begin treatment of osteoporosis in childhood in order to minimize bone loss during life [12].

Preventive stabilization or augmentation of the contralateral hip during ipsilateral hip fracture surgery on the other hand could be an instantly available modality to reduce the incidence of second hip fracture surgery in the high-risk patient. In a recently published study, we showed that elastomer femoroplasty (EF) prevents fracture displacement, however, the load to fracture was 10% percent lower in the femurs treated with EF [13]. Similar to previous biomechanical cadaver studies on proximal femur strength after implant removal, the decrease in load to fracture was attributed to the 10 mm diameter entrance hole in the lateral cortex [14].

Minimizing the entrance hole in the lateral cortex for EF using small entrance techniques could therefore reduce this decrease in load to fracture of the proximal femur.

Unpublished pilot studies pointed out that injection of elastomer into the proximal femur without drilling a hole in the cancellous bone does not result in a sufficient volume of elastomer to restore geometry after fracture. Therefore after drilling the entry hole in the lateral cortex, a channel has to be created in the proximal osteoporotic femur to suit the elastomer. Two techniques are possible: drilling a hole using an excentric drill or cancellous bone compression similar to kyphoplasty. The aim of the current study is to evaluate the effect of a 3.5 mm hole in the lateral cortex of the proximal femur with respect to the load to fracture. Furthermore two different EF techniques are compared, an excentric drill excavating technique and cancellous bone compression technique.

MATERIALS AND METHOD

A total of 16 pairs of osteopenic or osteoporotic femurs from human cadaveric donors were used. Five donors were male and 11 donors were female. The mean age of the donors was 76.8 years (SD 11.4). All cadaver femurs were obtained from the Department

of Anatomy, Leiden University Medical Centre. Fixation and preservation of all cadavers was performed by injection of embalming fluid into the femoral artery, consisting of 36% formaldehyde (CH_2O) with a mixture of ethanol (C_2H_5OH), glycerin ($C_3H_5(OH)_3$), phenol (C_6H_5OH), potassium sulfate (K_2SO_4), sodium sulfate (Na_2SO_4), sodium carbonate ($NaHCO_3$), sodium nitrate ($NaNO_3$), and sodium sulfite ($NaSO_3$).

To exclude the presence of focal bone pathology, plain X-rays were made of all specimens. The femoral Neck-Shaft-Angle (NSA) was measured from the plain anterior-posterior radiograph of each femur. We calculated the degree of osteoporosis of each proximal femur using Dual-energy X-ray Absorptiometry (DXA) with a Discovery A, QRD scanner (Hologic Inc., Bedford, USA). All femurs were scanned in air. Osteopenia and osteoporosis were defined according to the WHO using T-scores of respectively < -1 standard deviation and < -2.5 standard deviation from the young adult mean value [15].

From each femur pair, one femur was randomly selected for femoroplasty; the contralateral femur of the same donor was used as a control. In the femurs selected for femoroplasty we used a regular electric drill to drill a 3.5mm hole with a standard Ø 3.5mm, length 165mm, drill bit (Synthes inc, Solothurn, Switzerland) in the lateral cortex and channel in the femur neck.

The femurs were than randomly assigned to two groups, group A and group B. In group A the cavity for EF in the femoral neck was created by compressing the cancellous bone with an inflatable balloon, KyphX Xpander inflatable bone tamp (Kyphon inc., Sunnyvale, USA). To make a solid 'anchor' in the femoral head we used the 20 mm excentric drill (fig1a). In group B the cavity for EF was created using a specially designed excentric drill set (Department of Fine Mechanics, Leiden University Medical Center) (fig 1b). We used a 15 mm excentric drill for the femoral neck followed

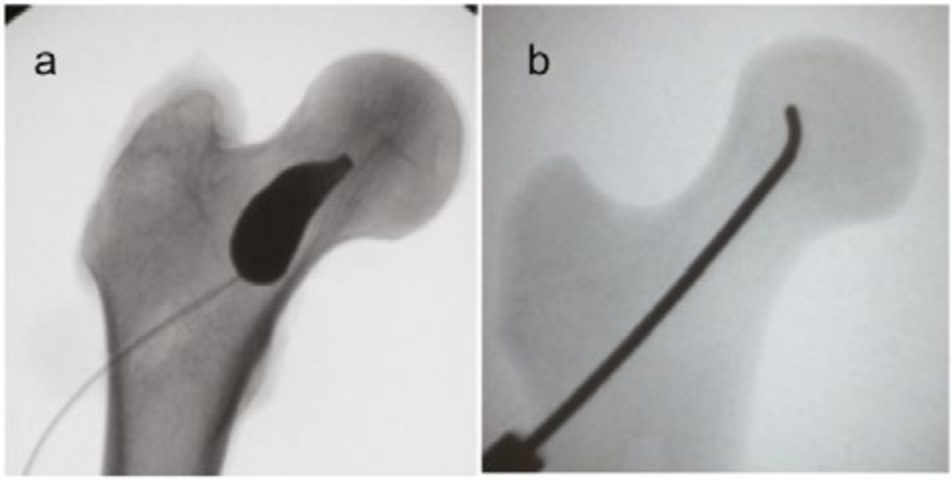

Fig 1*:* Example of the balloon compression technique, using a kyphoplasty balloon (a) and an example of the 20 mm excentric drill in the femur head (b)

by a 20 mm excentric drill to create the 'anchor' for the elastomer femoroplasty in the femoral head. To achieve reproducible cavities all femurs were drilled using fluoroscopy with a mobile X-ray machine (Pulsera® Mobile C-arms, Philips Healthcare, Eindhoven, The Netherlands). The drilled cavity was cleaned before EF by pulsed lavage system (Interpulse Stryker®, Kalamazoo, USA). Plain anterior-posterior and lateral radiographs and DXA-scans were made after drilling.

The elastomer used in the experiments is a two-component room-temperature addition-cure liquid silicone formulation, obtained from Viazym BV (ViaZym BV; Delft, the Netherlands). The two components consist off: A platinum containing vinyl-terminated polydimethylsiloxane (PDMS) with an optimized molecular weight with regard to viscosity versus mechanical properties of the cured end-product (elongation to break, modulus). This component further contains surface-treated amorphous silica and a sesquisiloxane-like material known as Vinyl Q, which increases tear-strength of the final cured elastomer without much increase in viscosity. The second component is a methylhydrodimethylsiloxane co-polymer containing vinyl-terminated PDMS. This component further contains surface-treated amorphous silica and Vinyl Q. PDMS is widely used *in vivo* because of its physiological inert properties [16, 17]. The elastomer we used was designed to have a low viscosity initially, to cure without exothermic heat, without the formation of by-products as it hardens (polymerization and cross linking) in a watery environment [18, 19]. The elastomer was injected into the proximal femur using a commercially available injector gun. The two components of the elastomer were mixed at room temperature using a static mixer attached to the nozzle of the injector gun.

Filling the proximal femur took place under fluoroscopy to evaluate the distribution of the elastomer in the proximal femur. We continued filling until either the elastomer overflowed from the lateral cortex hole or came out of vascular penetrations in the femur neck. All femurs were placed with the femoral head pointing down to prevent the silicon from running out while curing. Although the curing time of our silicone is approximately 10 minutes at room temperature all femurs were left to rest for 24 hours. During curing and in between examinations and tests the femurs were kept moist with cloths drenched in formaldehyde mixture. Plain radiographs were made to record the distribution of Elastomer.

Treated and control femurs were biomechanically tested using a material test machine (LR5KPlus 5 kN,Lloyd Instruments, Fareham Hants, UK) with a load-cell (XLC-50K-A1 Lloyd Instruments, Fareham Hants, UK) and material test and data analysis software (NEXYGEN*Plus,* Lloyd Instruments, Fareham Hants, UK*)* with a data acquisition rate of 8kHz. All femurs were fractured by simulating a fall on the greater trochanter in a modified Hayes-fall configuration [20]. The femoral shaft was firmly held by a steel arm in a 20-degree angle from the horizontal plane and with the femur head 15 degrees internally rotated (Figure 2).

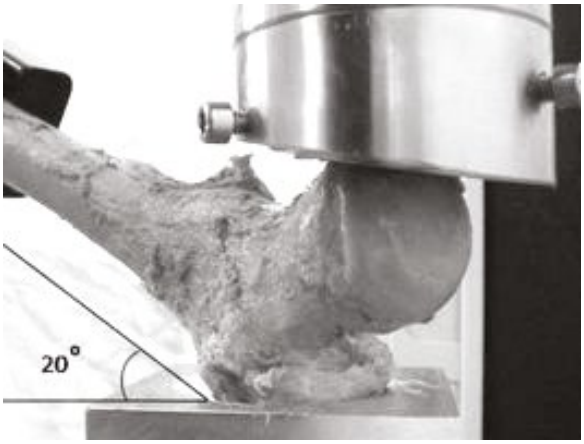

Fig 2. Modified Hayes-fall configuration. The femur is fixed at an angle of 20° with the horizontal plane simulating a fall on the greater trochanter.

The load was applied using a silicone-coated cup attached to the crosshead of the testing machine. The crosshead moved with a speed of 2mm/s and stopped when a 75% reduction in peak load was recorded by the load cell. The recorded load was defined as fracture load. After each specimen was fractured plain anterior-posterior radiographs were made to calculate the NSA. In case of complete displacement of the fracture we defined the NSA as 180 degrees.

After biomechanical testing the proximal femurs were immersed in sulphuric acid (H2SO4) until all cadaveric tissue was dissolved, and elastomer casts were left. The Elastomeric casts were rinsed thoroughly and volumes were measured by water immersion.

Statistical analysis of the data was done using SPSS (SPSS 16.0, SPSS Inc., Chicago, IL, USA). Paired student–T tests were performed to determine significance in fracture-load, load until displacement and NSAs, calculating *P*-values and 95% confidence intervals. *P*-values of <0.05 were accepted as significant. Correlation between fracture load and DXA results, and the correlation between fracture load and elastomer volume was determined by calculating the Pearsons (r) correlation.

RESULTS

The results of all treated femurs were compared to paired controls. Therefore, the treated and control femurs were similar with respect to age, bone mineral density (BMD) and NSA (Table 1).

Out of the sixteen femur pairs 18 femurs were osteopenic with a T score < -1 and > -2.5 (5 pairs in group A and 4 pairs in group B) and 14 femurs were osteoporotic with a T score < -2.5 (3 pairs in group A and 4 in group B). The average T-score was -2.4 (SD 0.8) in group A and -2.6 (SD 0.7) in group B. DXA-scans made after excavation of the

Table 1. Baseline characteristics of all cadaver femurs before fracturing

	Group A ***Balloon technique***		**Group B** ***Drill technique***	
	Control Mean (SD)	**EF Mean (SD)**	**Control Mean (SD)**	**EF Mean (SD)**
BMD	0.655 g/cm^2 (0.126)	0.668 g/cm^2 (0.107)	0.654 g/cm^2 (0.118)	0.633 g/cm^2 (0.090)
T-score	-2.44 (0.74)	-2.35 (0.81)	-2.488 (0.83)	-2.64 (0.68)
NSA	130 ° (5)	128 ° (5)	129°(6)	130°(6)

proximal femur for femoroplasty showed no significant decrease in T-score -2.0 (SD 0.9) in group A and -2.3 (SD 0.7) in group B.

Fracture loads for each femur in both groups are displayed in Table 2. In group A, the mean fracture load in the simulated fall configuration was 2904 N (SD 1091) for the controls versus 2803 N (SD 627) for the EF treated femurs (*P*= 0.742, 95% CI of the difference: -799 N – 597 N). This is a 3.5% drop in fracture load after EF treatment. The correlation coefficient between BMD and fracture load for the controls was r = 0.81 and for EF femurs was r = 0.79.

In group B the mean fracture load in the simulated fall configuration was 2773 N (SD 747) for the controls versus 2597 N (SD 834) for the EF treated femurs (*P*= 0.534, 95% CI of the difference: -809 N – 458 N). This is a 6.3% drop in fracture load after treatment. The correlation between BMD and fracture load for control femurs was r = 0.45 and for the EF treated femurs r = 0.95.

The NSAs measured on plain anterior-posterior radiograph before and after fracture in both groups are displayed in figure 3 and 4. The controls of femur pair 6,7 and 8 from group A and the controls of femur pair 3, 4, and 5 were completely displaced after fracture and were scored as 180° NSA.

Table 2. Fracture load in Newton for both control and EF treated femurs in Group A and B

	Group A ***Balloon technique*** *Fracture Force (N) in simulated fall configuration*		**Group B** ***Drill technique*** *Fracture Force (N) in simulated fall configuration*	
Femur pair	**Control**	**EF**	**Control**	**EF**
#1	1817	2314	1820	1217
#2	1846	1522	2643	1813
#3	2008	3146	3513	2300
#4	2794	2807	2462	2400
#5	2726	2943	3210	3151
#6	4963	3207	2043	3288
#7	3276	2942	2480	2839
#8	3804	3546	4010	3770
Mean (SD)	**2904 (1091)**	**2803 (627)**	**2773 (747)**	**2597 (834)**

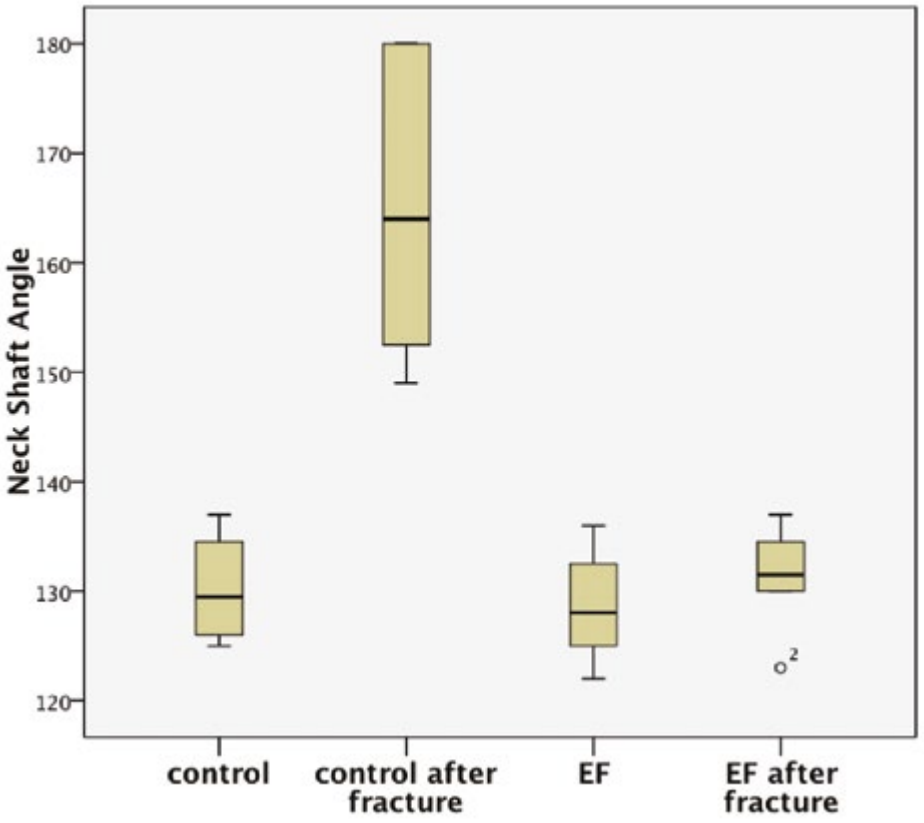

Fig 3. Boxplots of Neck Shaft Angle's (NSA) in control femurs and elastomer femoroplasty treated femurs, before and after fracture in group A (balloon femoroplasty).

In group A the mean NSA of the control femurs before fracture was 130° (SD 5) and after fracture 165° (SD 14). This is a mean displacement (ΔNSA) of 35°. In the EF treated femurs the mean NSA before fracture was 128° (SD 5) and 132° (SD 4) after fracture. This is a ΔNSA of 4° ($p < 0.001$, 95% CI of the difference 21°- 43°). In group B the mean NSA of the controls before fracture was 129° (SD 6) and after fracture 167° (SD 13). This is a ΔNSA of 38°. In the EF treated femurs the average NSA before fracture was 130° (SD 6) and 138° (SD 17) after fracture. This is a ΔNSA of 8° ($p < 0.001$, 95% CI of the difference 16° - 43°). There were 2 outliers one in each group. In group A, EF treated femur number 2 after fracture had an outlying NSA of 123° but did not differ significantly from its pre-fracture NSA of 122°. In group B, EF treated femur number 3 failed after fracture and was scored at 180° and therefore had an outlying observation.

The mean volume of elastomer in group A, 18.5 ml (SD 2.4) was significantly higher than in group B 14.5 ml (SD 2.7), P=0.05 (95% CI -0.02 – 7.97 ml). The correlation between fracture load and volume in group A was r = 0.60, and group B, r = -0.47 both correlations were statistically non-significant.

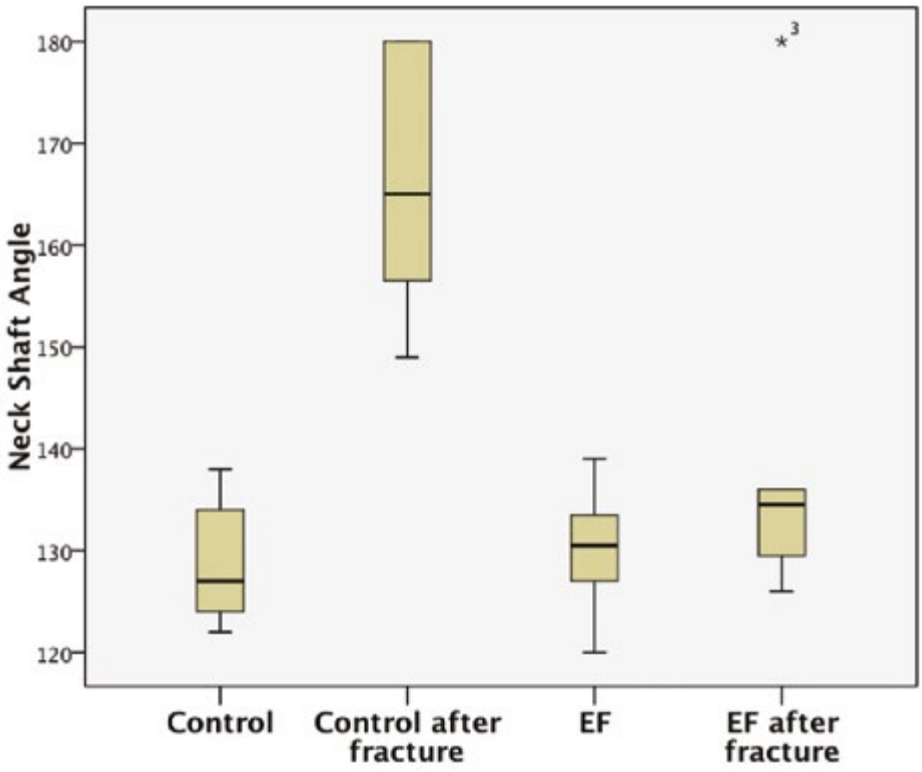

Fig 4. Boxplots of Neck Shaft Angle's (NSA) in control femurs and elastomer femoroplasty treated femurs, before and after fracture in group B (drill femoroplasty).

DISCUSSION

Elastomer femoroplasty of the proximal femur is a new and promising preventive strategy to reduce the increasing demand on healthcare resources of hip fractures and their sequelae. We showed that EF prevents displacement of the fracture according to NSA. Out of the 16 femurs treated with EF only one femur failed and had complete displacement. The fracture in this femur ran through the femur head of both the treated and paired control femur. The elastomer had insufficient grip to prevent displacement in this case.

In addition to the prevention of displacement the results of this study show a positive effect of minimal invasive elastomer femoroplasty on the fracture load, diminishing the possible EF induced fracture risk that we saw in our previous study. In this previous study we drilled a 10 mm diameter entrance in the lateral cortex and found a 10% decrease in fracture load. The major difference with our present study is that we drilled a smaller, 3.5 mm diameter, entrance hole. It is likely that the non-significant reduction in fracture load decrease after EF in our current experiment (3.5%

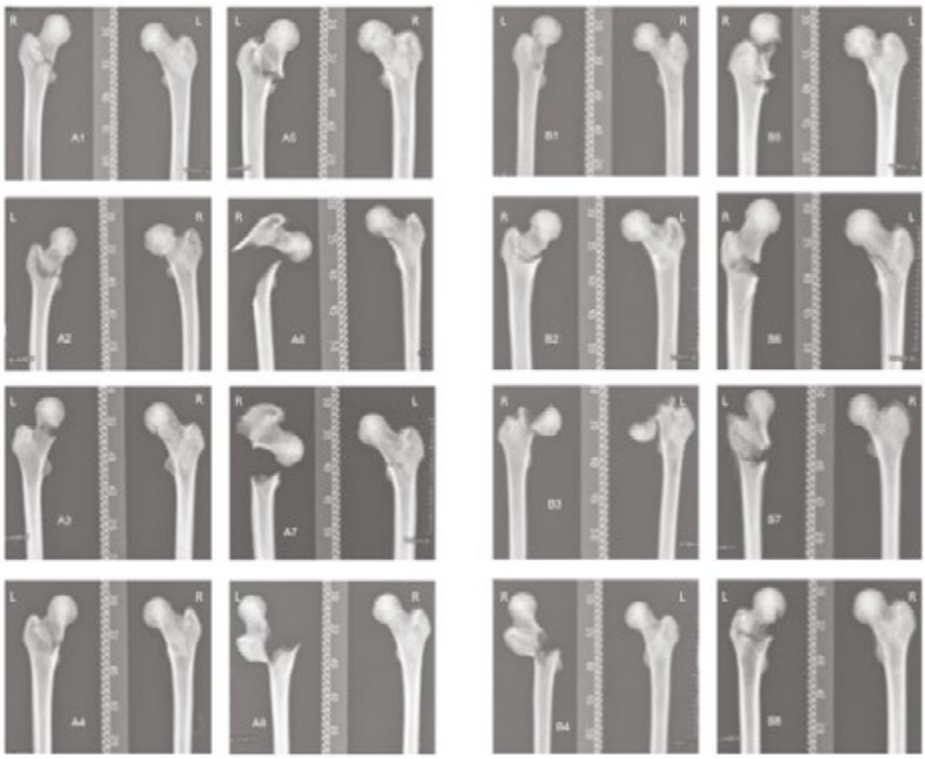

Fig 5. Plain anterior posterior radiographs after fracture. Some of the radiographs are mirrored so that the EF treated side is projected on the right hand side of the picture. The correct sides are displayed in the upper corners of each radiograph, and are marked by L and R. Femur pair B3 is the only pair with a complete failure of the EF treated femur.

for the balloon and 6.3% for the drill technique) can be contributed to the smaller diameter of the entrance hole. In vivo this 3.5 mm defect in the lateral cortex would close due to bone formation within a short period of time.

However the results of the fracture loads have to be interpreted cautiously. Since there was a large spread in fracture loads between femur pairs and between treated and control femurs from the same pair a statistical type 2 or beta error could be possible. A possible explanation for this large spread in fracture loads could be the differences in hip geometry between pairs and individual proximal femurs. Previous studies using cadaveric materials also found large standard deviations in the load to fracture [13, 21]. In future experiments with EF this large spread in fracture loads could possibly be decreased by using standardized composite bones.

We used fixed specimens for our experiments. This is a limitation of our study since most biomechanical experiments are done with fresh frozen cadaveric bones. We justified this second choice material because each femur was tested to its native, fixed control. The results from the DXA-scans show that in our experiments the drilling of a hole and excavation of the proximal femur has no significant negative effect on

measured BMD. This suggests that DXA does not accurately assess the cancellous bone mass. Since the femurs in both control and treated groups did not significantly differ in fracture load, the role of cancellous bone on proximal femur strength is uncertain in these fixed cadaver femurs.

Reduction of hip fracture incidence by preventive EF is unlikely since EF does not increase fracture loads. However hip fracture surgery could be reduced since EF prevents the displacement of fracture elements according to NSA. Conservative functional treatment of these undisplaced hip fractures, with early reactivation and mobilization, can than be administered. This will diminish hip surgery related complications. Furthermore the mortality rate after conservative functional treatment as has been described after Garden 1 hip fractures is significantly lower compared to surgery [22, 23].

The polydimethylsiloxane elastomer we used is not a particularly stiff material like steel or regular cement. Increasing the strength of the proximal femur to reduce hip fracture incidence by augmentation or enhancement with injectable cement (Femoroplasty) has been proposed [21]. However, in case of a fall the energy is passed on to parts of the hip with no augmentation like the femur shaft or acetabulum. A fracture in those regions often requires more extensive surgery with subsequent increased morbidity and mortality [24-26]. On the other hand continuous loading and unloading in a fractured femur after EF stabilization could cause movement in the fracture leading to complications like delayed or malunion. In such cases or in the case of secondary fracture dislocation, osteosynthesis by implantation of a Dynamic Hip Screw or gamma-nail should not be a problem. Normal drills and instruments can easily penetrate the EF-treated hip. This is a major advantage over cement.

Although rare, avascular necrosis occurs in the conservatively treated undisplaced hip fractures in 2-11% [22, 23]. This could be a possible drawback of preventive EF. We also know that cement augmentation in unstable pertrochanteric fracture does not cause an increase in avascular necrosis [27]. Future studies should clarify the effect of EF on the vasculature of the femur head and proximal femur.

The balloon technique created a significantly greater cavity for the elastomer, however this did not result in significant differences in fracture loads or NSA between both groups. The quantity of the elastomer in the proximal femur did not significantly correlate with fracture load in either group. Again future experiments with standardized composite bones could overcome the difficulty of the large spread in fracture loads.

From our previous experiments we know that displacement forces after EF tested in a single leg stance configuration are approximately 1500N. Hip-contact forces with walking in a normal gait pattern are higher, ranging from 1500-2250N in a 75 kg individual [28-30]. However after hip fracture surgery patients start to mobilize using walking aids and thus only loading with a smaller portion of their body weight. Moreover, pain after a hip fracture of an EF stabilized hip, will probably also restrict the

patient from full weight bearing. This would reduce the load of force and therefore reduce the risk of secondary displacement of the fracture elements, allowing impaction and consolidation. Future cyclic loading and unloading tests in fractured femurs treated with EF will have to clarify these displacement forces.

We found that EF reduced even complex trochanteric fractures to normal geometry. However in vivo these instable, extra-capsular fractures are more likely to have secondary displacement after load bearing. Therefore, a careful selection of patients who are likely to acquire a transcervical fracture in the future should be made. Since the likelihood of identical fractures in both hips is as high as 75% [11, 31]. High-risk patients with a transcervical hip fracture could be considered for preventive EF in their contralateral hip during primary hip fracture surgery.

In conclusion this study shows that elastomer femoroplasty stabilizes the proximal femur by restoring hip geometry according to NSA after fracture. Furthermore minimal invasive balloon and excentric drill femoroplasty techniques did not reduce fracture force compared to paired control femurs. However these results have to be interpreted cautiously since sample size was small and standard deviations were high. Minimal invasive elastomer femoroplasty could be a promising new strategy to prevent hip fracture surgery. Future experiments should clarify its feasibility in-vivo.

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CHAPTER 7

Cyclic loading of fractured cadaveric femurs after elastomer femoroplasty: An in vitro biomechanical study

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ABSTRACT

Elastomer femoroplasty is a novel and experimental approach in the prevention of hip fracture surgery. Previously, we published the results of an in vitro cadaveric experiment in which we showed a significant reduction of fracture displacement in treated femurs. The aim of the present study was to establish the failure loads and interfragmentary movement of fractured, elastomer femoroplasty treated, femurs during cyclic loading.

Methods

16 cadaveric femurs were treated with elastomer femoroplasty and fractured in a simulated fall configuration. Each specimen underwent 10 cycles with a preload of 50 N, starting with a peak load of 250 N followed by 10 cycles of 500N and continued with 500N increments. The crosshead speed was 2 mm/s. The failure load, the number of completed cycles and crosshead extensions were recorded.

Findings

The mean failure load was 2709 N (SD 1094). The number of completed cycles until failure was 60 (SD 22). The mean translation during maximum loading was 5.25 mm (SD 0.9). At 1500 N (two times the bodyweight of a 75 kg individual) the extension was 3.16 mm.

Interpretation

Preventive elastomer femoroplasty leads to stabilization of the proximal femur after fracture. In a single leg stance configuration, cyclic loading with mean failure loads that well exceed the peak loads during normal gait is feasible.

INTRODUCTION

After an initial hip fracture patients have a 10% risk of acquiring a second, contralateral hip fracture in the first year and a lifetime risk that can be as high as 55% [1-3]. The introduction of countless preventive measures in the last three decades has not led to a decline in the incidence of second hip fractures [4, 5]. Furthermore the sequelae of a second hip fracture - i.e. higher morbidity and mortality compared to those related to a first hip fracture, a high complication rate and long-term disability requiring nursing home admissions - form a major burden on healthcare resources [6].

Recently we published the results of a biomechanical experiment on elastomer femoroplasty (EF): an entirely novel and experimental approach in the prevention of hip fracture surgery [7]. The main objective of EF is not to prevent hip fractures, but to prevent fracture displacement and therefore the need for hip fracture surgery. In a static *in vitro* study using cadaveric femurs, we demonstrated that EF reduces fracture displacement after monotonic loading. In these femurs, hip geometry according to the Neck-Shaft-Angle (NSA) was maintained after fracture. In theory, these undisplaced hip fractures in elderly, low-demand patients could be treated conservatively with early mobilization and without surgery.

The conservative treatment of undisplaced hip fractures, Garden type 1 and 2, with early mobilization and reactivation is well established and can lead to fracture impaction and consolidation [8-11]. However, high rates of secondary displacement have been reported. Secondary displacement is best treated surgically, be it with added morbidity and mortality [12]. The elastomeric stent that is formed in EF primarily prevents displacement of the fracture parts. Theoretically, the elastomeric stent would not only reduce displacement of hip fractures at the time of injury, but might also contribute to a reduction in the secondary displacement rates during conservative treatment of undisplaced hip fractures. To be successful though, the fractured EF treated femurs would have to withstand considerable forces that are comparable to those on the proximal femur during normal gait. These peak contact loads are well described in the literature and range between 2.0 – 2.7 times body weight [13, 14].

We hypothesized that the load to failure of fractured, EF treated femurs during cyclic loading exceeds the peak load during normal gait. Furthermore, we measured the displacement, and determined the correlation of load with elastomer volume. Finally, we compared the results of intra-capsular and extra-capsular fractured EF treated proximal femur constructs.

MATERIALS AND METHOD

Cadaveric femurs

A total of 16 femurs (8 right, 8 left) were obtained from the Department of Anatomy, Leiden University Medical Centre. Eleven donors were female, 5 were male. The mean age was 76.8 (SD 11.4) years. Fixation and preservation of the cadavers was performed by injection of an embalming fluid into the femoral artery. The embalming fluid was produced by the Department of Anatomy, Leiden University Medical Centre, and consisted of 36% formaldehyde (CH_2O) with a mixture of ethanol (C_2H_5OH), glycerin ($C_3H_5(OH)_3$), phenol (C_6H_5OH), potassium sulfate (K_2SO_4), sodium sulfate (Na_2SO_4), sodium carbonate ($NaHCO_3$), sodium nitrate ($NaNO_3$), and sodium sulfite ($NaSO_3$).

Plain X-ray's were made of all specimens to exclude the presence of focal bone pathology. The femoral Neck-Shaft-Angle (NSA) was measured from the plain anterior-posterior radiograph of each femur. We measured the degree of osteoporosis of each proximal femur using Dual-energy X-ray Absorptiometry (DEXA) with a Discovery A, QRD scanner (Hologic Inc., Bedford, USA). All femurs were scanned in air. Osteopenia and osteoporosis were defined according to the WHO using T-scores of respectively < -1 standard deviation and < -2.5 standard deviation from the young adult mean value (1994).

After fracture, the proximal femurs were classified using the AO classification for proximal femur fractures. Sub trochanteric fractures and hip fractures that were completely displaced were excluded from cyclic testing.

Elastomer femoroplasty

The elastomeric compound, polydimethylsiloxane (PDMS, ViaZym BV, Delft, The Netherlands) was manually injected into the proximal femur using a commercially available, hand held injector gun (Mixpac, Sulzer, Haag, Switserland). PDMS is an elastomer composed of two components. It is widely used *in vivo* (e.g. for the augmentation of nasal and chin bones) because of its physiological inert properties [15, 16]. The elastomer we used was designed to have a low initial viscosity enabling injection through 8g needles. It cures without exothermic heat and without the formation of by-products as it hardens (polymerization and cross linking) in an aqueous environment [17-19].

Before filling, the femurs were prepared by drilling a 3.5 mm hole in the lateral cortex. A channel was made in the femur neck either with a 10 mm kyphoplasty balloon or a 10 mm excentric drill. Finally, a 15 mm excentric drill hole was made in the femur head to form an "anchor site" for the elastomer. After drilling, the hole was rinsed out using a pulsed lavage system (Stryker, Kalamazoo, Michigan, USA) and saline.

The two components of the elastomer were mixed at room temperature using a static mixer (Mixpac, Sulzer, Haag, Switserland) that is attached to the nozzle of an injector gun.

Filling the proximal femur continued until either the elastomer overflowed from the lateral cortex hole or exited vascular penetrations in the femur neck. All femurs were placed with the femoral head pointing down to prevent the silicon from running out while curing. Although the curing time of our silicone is approximately 10 minutes at room temperature all femurs were left to rest for 24 hours. During curing and in between examinations and tests the femurs were kept moist with cloths drenched in a formaldehyde mixture. Plain radiographs were made to record the distribution of the elastomer, which is a radiopaque material.

Hip fracture generation

Biomechanical testing was done using an LR5K*Plus* 5 kN load testing machine with a XLC-50K-A1 Load-cell and NEXYGEN*Plus* material test and data analysis software (Lloyd Instruments, Fareham Hants, UK). Fractures were generated by simulating a fall on the greater trochanter in a modified Hayes-fall configuration [20]. The femoral shaft was held firmly by a steel arm at a 20-degree angle from the horizontal plane and with the femur head 15 degrees internally rotated (Figure 1). The load was applied using a silicone-coated cup attached to the crosshead of the testing machine. The crosshead moved with 2mm/s and stopped automatically when the load cell registered an abrupt reduction in load of 75%. The recorded load was defined as fracture load. After each specimen was fractured plain anterior-posterior radiographs were made to calculate

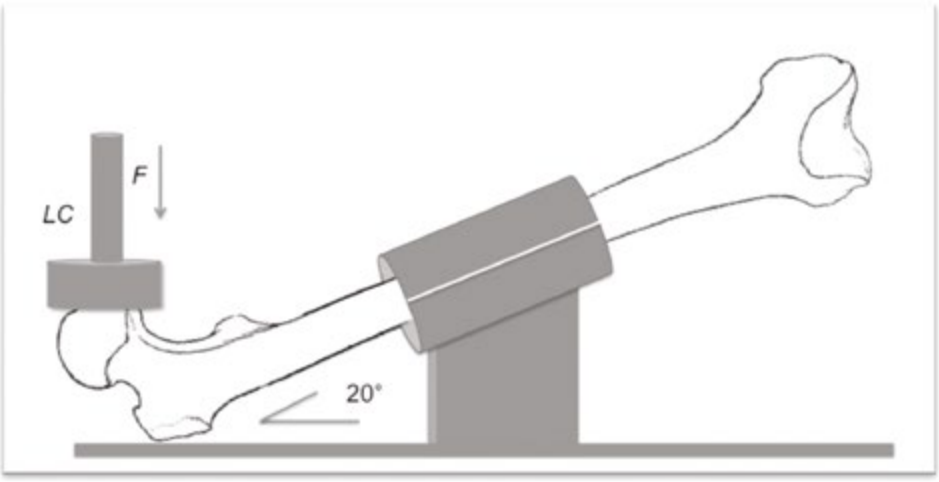

Fig 1. Schematic display of simulated fall configuration used to generate hip fractures, after Courtney et al, 1995. The femur shaft is angled 20-degree from the horizontal plane, internally rotated 15 degrees. The load cell (LC) is attached to the crosshead of the tensile testing machine and travels with 2 mm/s.

the NSA. In case of complete displacement of the fracture we defined the NSA as 180 degrees.

Construct stability

Cyclic axial loading to failure was then performed using the same tensile testing machine with stance-like load configuration (Frankel 1960) [21]. Each femur was cut 20 cm distal to the lesser tubercle and was cemented in a polyethylene cylinder using poly(methyl methacrylate) (PMMA) (Biomet Inc, Warsaw, IN). The femur with polyethylene cylinder was placed in a stainless steel holder and load was applied to the femoral head and directed within the coronal plane at 20° to the shaft axis (Figure 2).

Starting with a 50 N preload, each specimen was subjected to 10 cycles of loading from 50 N (minimum) to 250 N (maximum), followed by 10 cycles of loading from 50 N to 500 N. After successful completion of the 50-500 N series, the maximum

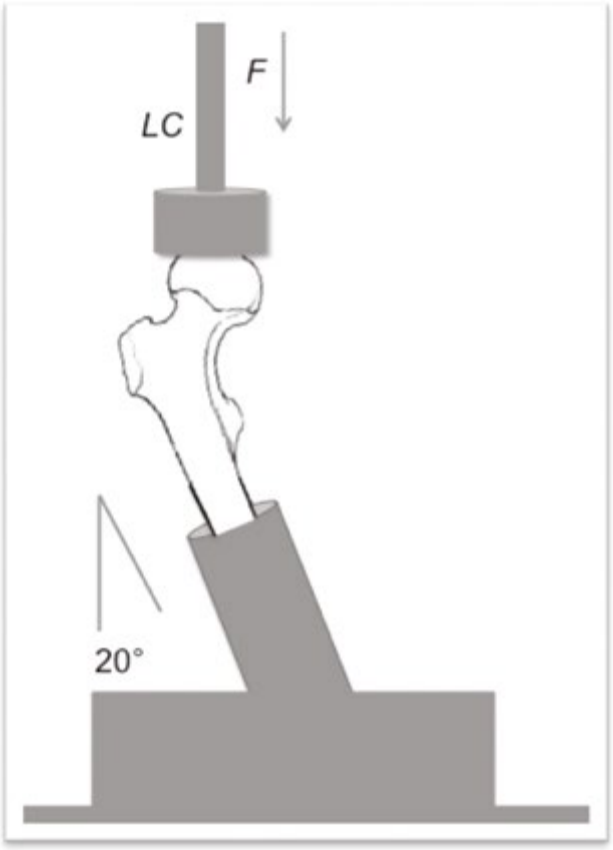

Fig 2. Schematic display of stance-configuration used to evaluate mechanical behavior of EF-augmented fractured femurs subjected to cyclic loading. In this configuration the femoral shaft is oriented 20-degrees from the vertical in the axial plane. The load cell (LC) is attached to the crosshead of the tensile testing machine and travels with 2 mm/s. During testing, the maximum load was incremented onwards (by 250 or 500 N) after every tenth cycle.

load was increased 500 N every ten cycles (i.e. to 50-1000 N, 50 - 1500 N, 50 - 2000 N, etc.) until failure. Failure was defined as either a decrease in the NSA of more than 5 degrees as measured after every 10 cycles, or an abrupt reduction of 50% in the applied load as registered by the load cell during any given cycle. The maximum output load that resulted in the 5 degrees decrease in the NSA or the 50% reduction in applied load was defined as the failure load. The difference in the NSA before and after cyclic loading was visually measured with a transparent protractor at the end of the last cycle with the crosshead returned to its 50 N preload position. The lines through the center of the femur shaft and running through the center of the head and de femur neck were used as landmarks. All cyclic loading was performed using a triangular waveform, with crosshead speed of 2 mm/s.

Elastomer volume assessment

After cyclic testing the proximal femur was sawn off just below the lesser tubercle. The proximal femurs were submersed in sulphuric acid (H_2SO_4) until all cadaveric tissue was dissolved and only elastomer casts were left. The elastomeric casts were rinsed thoroughly and volumes were measured by water immersion. Correlation of the volume of elastomer to the fracture load, failure load, number of cycles and maximal extension was then calculated.

Statistical analysis

Statistical analysis of the data was done using SPSS (SPSS 16.0, SPSS Inc., Chicago, IL, USA). Descriptive analyses were used to determine mean and standard deviations of fracture load, failure load and maximal extension at 1500 N in all femurs. Paired student–T tests were performed to determine significance in failure load and maximal extension between intra-capsular and extra-capsular fractures, calculating *P*-values and 95% confidence intervals. *P*-values of <0.05 were accepted as significant. Correlation between fracture load and elastomer volume, between failure load and elastomer volume, between number of cycles and elastomer volume and between maximal extension and elastomer volume were determined by calculating the Pearson's (r) correlation coefficient.

RESULTS

Fractured femurs

A total of 16 cadaveric femurs treated with EF were fractured using the modified Hayes-fall configuration. However, only 14 femurs were tested using the cyclic loading protocol

as 2 of the induced fractures were inherently unstable: one was subtrochanteric, and the second fracture included a fracture through the femoral head.

The mean BMD of the tested femurs (n = 14) was 0.67 g/cm^2 (SD 0.09) and the mean T-score was -2.39 (SD 0.69). The mean fracture load was 2813 N (SD 683). Neck-Shaft-Angle before fracture 129 degrees (SD 4.5) and after fracture 133 degrees (SD 3.3). AO classification: 5 fractures were classified as intra-capsular, 31-B1 and 9 fractures were classified as extra-capsular, 31-A1 (n=5) A2 (n=1) and A3 (n=3). The baseline characteristics of the femurs divided by fracture location are displayed in Table 1. The NSA before fracture was significantly higher in the intra-capsular fractures 133 degrees (SD 2.3) versus 127 degrees (SD 4.4) in the extra-capsular fractures (*P*= 0.03, 95% CI 0.6 – 9.9).

Table 1. Baseline characteristics.

	Total (n=14) Mean (SD)	**Intra capsular fracture (n=5)** Mean (SD)	**Extra capsular fracture (n=9)** Mean (SD)	**P**	**95% CI of the difference**
Age (years)	76 (9.9)	75 (9.4)	77 (13.6)	0.68	-15.0 – 10.0
Gender, *m : f*	5 : 9	1 : 4	4 : 5		
BMD (g/cm^2)	0.67 (0.09)	0.65 (0.10)	0.67 (0.10)	0.74	-0.13 – 0.10
NSA before fracture (°)	129 (4.5)	133 (2.3)	127 (4.4)	0.03	0.6 – 9.9
NSA after fracture (°)	133 (3.3)	135 (2.3)	131 (3.4)	0.78	-0.4 – 7.0
Fracture loads (N)	2813 (683)	2674 (955)	2890 (532)	0.59	-1 – 637
Elastomer volume (cm3)	16.8 (3.3)	15.2 (4.1)	17.7 (2.6)	0.19	-6.4 – 1.4

Fracture stabilization

The results of cyclic loading are displayed in Table 2. None of the femurs failed due to a decrease in NSA of more than 5° measured in-between cycles. For the intra capsular fractures (AO classification 31-B 1-3, n=5) the mean number of completed cycles was 53 cycles (SD 24) and for the extra capsular fractures (AO class. 31-A 1-3, n=9) 64 cycles (SD 21) (*P*= 0.40, 95% CI -37 – 16). The mean failure load for the intra capsular fractures was 2399 N (SD 1339) and 2882 N (SD 978) for the extra capsular fractures (*P*= 0.45, 95% CI -2 – 867). The mean extension during maximal loading for the intra capsular fractures was 5.45 mm (SD 0.39) and 5.14 mm (SD 1.10) for the extra capsular fractures (*P*= 0.56, 95% CI -0.81 – 1.43).

At 1500 N the mean extension of the crosshead was 3.16 mm (SD 0.82). For the intra capsular fractures the extension was 3.25 mm (SD 1.29) and for the extra capsular fractures 3.12 mm (SD 0.54), (*P*= 0.77, 95% CI -0.97 – 1.27).

Elastomer volume

The mean volume of injected elastomer was 16.8 cm^3 (SD 3.3). The Pearson's correlation (R) between injected volume and fracture load was *r* = - 0.05, between volume and

failure load was r = 0.22, between volume and number of cycles was r = 0.32 and between volume and maximum extension was r = -0.30.

Table 2. Results of Cyclic Testing.

	Total (n=14) Mean (SD)	**Intra capsular fracture (n=5)** Mean (SD)	**Extra capsular fracture (n=9)** Mean (SD)	**P**	**95% CI of the difference**
Failure loads (N)	2709 (1094)	2399 (1339)	2882 (978)	0.45	-2 – 867
Completed cycles until failure	60 (22)	53 (24)	64 (21)	0.40	-37 – 16
Extension at 1500 N (mm)	3.16 (0.82)	3.25 (1.29)	3.12 (0.54)	0.77	-0.97 – 1.27

DISCUSSION

This study was performed to establish the feasibility of elastomer femoroplasty (EF) in stabilizing the proximal femur after fracture. To do so, we cyclically tested fractured human cadaveric femurs that were prophylactically treated with EF before fracture. Our outcome variables were failure load and displacement during cyclic loading. In our previous experiments we demonstrated that EF prevents displacement of the proximal femur at the time of fracture [7, 22]. The present study shows that the failure load of fractured femurs during cyclic loading was 2709 N. This well exceeds the peak loads of approximately 1500 – 2025 N during normal gait in a 75 kg individual [13, 14].

The main objective of preventive EF is to reduce the degree of fracture dislocation, thereby reducing the number of displaced hip fractures. There are extensive data on the functional treatment of undisplaced hip fractures, with early mobilization and without surgery. Secondary displacement rates of undisplaced hip fractures published in the literature range from 14-46% [8, 10, 11]. Early resumption, i.e. within 48 hours after fracture presentation, of partial or full weight bearing leads to a higher secondary displacement rate but decreases the number of complications associated with prolonged bed rest [8]. In a prospective study of 247 patients, Cserhati et al discerned 16% of general complications with bed rest versus 3% for direct surgical stabilization [12]. In the present in vitro cadaveric femur experiment we found that secondary displacement of the undisplaced hip fractures occurred after cyclic loading with forces that well exceed the peak loads during normal gait. After regular hip fracture surgery or hemiartroplasty these peak loads could be considerably lower since post-operative pain constrains the patient from full weight bearing [23]. In fact Koval et al concluded that elderly patients who are allowed to bear weight as tolerated after operative treatment of a fracture of the femoral neck or an inter trochanteric fracture, appear to voluntarily limit loading of the injured limb to 51% during the first post-operative week [24]. These patients have to be stimulated to walk and are prescribed pain relief medication to gradually reach 87% loading at 12 weeks. Comparable pain and consequent limited peak loads could theoretically be expected after hip fracture in an EF stabilized hip, diminishing the risk of secondary displacement. However, in

the event that EF fails to stabilize the fracture parts and secondary displacement does occur, or fracture healing is impaired in any other way, it would remain possible to stabilize the fracture with standard surgical osteosynthesis. We found that normal drills and prostheses can easily be used after EF. Further experiments will have to be done to evaluate the potential debris and its biological response after drilling in the elastomer filled proximal femur.

We did not measure the exact inter-fragmentary movement. It is possible that the measured crosshead extension was an overestimate of the true inter-fragmentary movement due to flexibility in femur shaft and the stainless-steel stance-construct. Further in vitro experiments should be done to measure the exact movement in the fracture during loading.

Inter-fragmentary movement during loading and unloading could lead to pseudarthrosis, pain and an increase in immobility. On the other hand inter-fragmentary movement also leads to increased callus fracture healing [25]. Therefore the dynamic fixation of fractures with minimally invasive surgical techniques, such as intra-medullary nailing, has become increasingly popular. These well-established techniques also lead to relatively large fracture gaps (larger than 5 mm) and considerable inter-fragmentary movements (0.2-5 mm) [26].

We did not find any statistically significant differences in the failure load or extension between intra capsular and extra capsular fractures. Beforehand we expected that latero-caudal fractures, i.e. extra capsular fractures, would benefit less from EF stabilization, considering the relatively medial position of the elastomer in the proximal femur. The absence of significant differences might either suggest that the elastomer inter-digitised in the trochanteric cancellous bone and thus created extra grip and stabilization, or that the design of the experiment was unable to show the difference between intra and extra capsular fractures. Further experiments are needed to determine whether EF treatment should be limited to those individuals that are expected to acquire an intra capsular second hip fracture. In that case, patient selection based on type and location of the primary fracture would be easy and reliable since second, contralateral hip fractures are identical to the first hip fracture in 75% of the cases [27].

There were certain additional limitations in our study design. First, there was no comparison of the performance of fractured EF treated femurs vs. controls. Fractured femurs that were not treated with EF were all completely dislocated and were therefore excluded from cyclic testing [7]. Future experiments should be performed to compare EF with other invasive preventive techniques. Another limitation is that we chose to perform our DEXA scanning in air rather than water. The main objective of the DEXA scans in the present study was to detect any outliers in the group rather than establish the exact t-score as a definition of osteoporosis. Furthermore, we used fixed specimens

instead of fresh frozen cadaveric bones. We justified this choice of material because each femur was tested to its native, fixed control in the simulated fall.

In this in vitro cadaver study the femoral shafts and heads were constrained by our set-up. This is a simplification of the in vivo post fracture situation and could enhance progressive impaction of the fracture. The soft tissue and hip capsula that are present in vivo might add to the stability of the fracture. On the other hand, muscles and ligaments could cause rotational and distractive forces on the proximal hip. We did not test these forces in our in vitro experiment but they could lead to secondary displacement and therefore failure of the EF stabilization.

When considering preventive EF in vivo the following issues should be discussed. Preventive EF in itself could increase the risk of second hip fracture. In our previous studies we found that EF resulted in a decrease of 5%-10% in load to fracture in a simulated fall configuration, though with the sample size we used, we failed to reach statistical significance. We attributed this possible decrease in fracture load to the 3,5 mm entrance in the lateral cortex. If this is the case in vivo the fracture risk after EF might diminish with the healing of the entrance hole over time. However, EF remains an invasive technique with possible complications including emboli, infection and hematoma. Furthermore, there is a risk that preventive EF does not result in second hip fracture healing. Therefore, only patients with a high risk of second fracture should be selected for preventive EF during first-hip-fracture surgery. Risk factors including female gender, older age, cognitive impairment and lower bone mass could be used in selecting these patients [1].

In conclusion, this in vitro cadaveric biomechanical study showed that EF prevents fracture displacement as assessed by the NSA, confirming our previous experiments. Cyclic loading of these undisplaced, geometrically unchanged hip fractures is feasible with failure loads that exceed the peak loads of normal gait. The limited inter-fragmentary movement and consequent risk of non-union will have to be quantified in future studies.

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CHAPTER 8

Feasibility of osteosynthesis of fractured cadaveric hips following preventive elastomer femoroplasty

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ABSTRACT

Background

In vitro cadaveric studies showed that elastomer femoroplasty (EF) prevents displacement of fracture parts after proximal hip fracture allowing for non-operative treatment. In the event that secondary displacement does occur, the purpose of the present study was to determine the feasibility of performing osteosynthesis of a fractured hip that has been treated with EF.

Methods

Ten pairs of human cadaveric femurs were fractured in a simulated fall configuration. From each pair, one femur was randomly selected for EF prior to fracture generation and the contralateral femur was used as control. Following hip fracture generation, osteosynthesis was performed in all femurs and the operative time, technical difficulties during the procedure, and postoperative failure-load were recorded.

Results

The mean (SD) time to perform osteosynthesis was 20 (6) minutes in the control-group and 19 (5) minutes in the EF-group (P= 0.69). During osteosynthesis of the fractured hip in the EF-group, no difficulties (including the need for additional instruments to remove elastomer from the proximal femur) were recorded. Postoperative failure-load was similar in the control-group and the EF-group.

Conclusion

Fixation with routine osteosynthesis of displaced cadaveric hip fractures is not hindered by the presence of previously injected elastomer.

INTRODUCTION

Among survivors of an initial hip fracture, up to 16% of elderly patients are at increased risk of sustaining a second, contralateral hip fracture [1, 2]. The risk of a second hip fracture increases with age [1, 2], weakened cognitive and motor function [3], respiratory disease [4] and solitary life [5]. Recent literature suggests that the outcome of surgery for a second, contralateral fracture may be worse than that of a first hip fracture [6-8] in terms of early postoperative complications, discharge institutionalization, independent mobility and survival [6].

Given the detrimental impact of a second hip fracture on elderly patients, different strategies have been proposed to prevent the sequential trauma, including pharmaceutical treatment for osteoporosis [9-11], external mechanical protection with hip protectors [12], and cement augmentation of osteoporotic bone [13, 14]. The injection of cement into osteoporotic cadaveric proximal femurs resulted in an 82% increase in peak fracture loads for a simulated fall on the hip, compared to non-injected femurs [15]. However, cement augmentation is associated with significant heat generation due to polymethyl-methacrylate polymerization. The exothermic reaction of cement could cause thermal necrosis of healthy bone and potentially lead to avascular necrosis of the femoral head [16, 17]. In addition, osteosynthesis of fractured femurs that were beforehand reinforced with cement may be challenging, with particular difficulty recorded in the removal of the composite [13].

We recently introduced the concept of elastomer femoroplasty (EF), i.e. preventive stabilization with elastomer, injected in the contralateral femur during ipsilateral hip fracture surgery [18-20]. Unlike cement augmentation, the intention of EF is not to prevent the occurrence of a second, contralateral fracture. In fact, fracture loads of EF-treated cadaveric femurs were approximately 10% lower than those of non-augmented femurs [18]. Rather, EF has been shown to prevent displacement of the fracture as measured with the Neck Shaft Angle (NSA) directly after impact. Similar to the well-established conservative treatment of undisplaced hip fractures, Garden types 1 and 2 [21], the prevention of fracture displacement by EF at the time of injury could result in primary fracture healing, thereby eliminating the need for a surgical intervention in these often, frail elderly patients. In addition, EF has been shown to prevent secondary displacement of the fracture during subsequent cyclic loading of cadaveric femurs [19, 20]. In the event that EF fails to stabilize the fracture parts and secondary displacement does occur, fracture fixation with routine osteosynthesis should remain possible and equally stable compared to hip fractures without preventive EF. The objective of the present in-vitro biomechanical study was to determine the feasibility of performing osteosynthesis of a fractured proximal femur that has been treated with EF and its subsequent construct stability. We hypothesized that there is no difference in surgical time, difficulty in performing the osteosynthesis, or failure load after osteosynthesis of

fractured proximal femurs that were stabilized with elastomer femoroplasty (EF-group) and fractured proximal femurs without elastomer femoroplasty (control group).

METHODS

Cadaveric femurs

Ten pairs of human cadaveric femurs from donors with a mean age of 81 years (SD 7.6 years) were obtained from the Department of Anatomy, Leiden University Medical Centre (LUMC). Five donors were male and five donors were female. Preservation of the cadavers was performed by injection an embalming fluid into the femoral artery. The embalming fluid consisted of 36% formaldehyde (CH_2O) with a mixture of ethanol (C_2H_5OH), glycerin ($C_3H_5(OH)_3$), phenol (C_6H_5OH), potassium sulfate (K_2SO_4), sodium sulfate (Na_2SO_4), sodium carbonate ($NaHCO_3$), sodium nitrate ($NaNO_3$), and sodium sulfite ($NaSO_3$).

Plain radiographs were made of all specimens to exclude the presence of focal bone pathology. The femoral neck shaft angle (NSA) was measured from the plain anteroposterior radiograph of each femur using IQ-view web-viewer (V2.1.0, Image Information Systems Ltd., London). We calculated the degree of osteoporosis of each proximal femur using dual-energy X-ray absorptiometry (DXA) with a Discovery A, QRD scanner (Hologic Inc., Bedford, USA). All femurs were scanned in air. Osteopenia and osteoporosis were defined according to the WHO using T-scores of, respectively, < -1 standard deviation and < -2.5 standard deviation from the young adult mean value (Report WHO Study Group, 1994).

Elastomer Femoroplasty

From each pair, one femur was randomly selected for elastomer femoroplasty (EF-group, n=10). The contralateral femurs were used as control (control-group, n=10). Mean (± SD) bone mineral density (BMD) was 0.703 g/cm^2 (0.111) in the control group and 0.702 g/cm^2 (0.120) in the EF-group, respectively. Mean (± SD) *T*-score, a score used to express BMD in standard deviation from the mean BMD of a young adult, was -2.14 (0.74) in the control group and -2.14 (0.81) in the EF-group, respectively. The mean (± SD) NSA in the control group was 129˚ (3) compared to 128˚ (4) in the EF –group.

Elastomer femoroplasty was performed as described in detail previously [18]. The femurs were prepared by drilling a 3 mm hole in the lateral cortex. A channel was made in the femur neck with a 10 mm excentric drill. Finally, a 15 mm excentric drill hole was made in the femur head to form an "anchor site" for the elastomer. After drilling, the hole was rinsed out using a pulsed lavage system (Stryker, Kalamazoo, Michigan, USA) using a saline solution. The elastomeric compound, polydimethylsiloxane (PDMS,

ViaZym BV, Delft, The Netherlands), was manually injected into the proximal femur using a commercially available, hand held injector gun (Mixpac, Sulzer, Haag, Switzerland). PDMS is an elastomer that has a low initial viscosity, cures without exothermic heat and without the formation of by-products as it hardens in an aqueous environment [22, 23]. Filling the proximal femur continued until either the elastomer overflowed from the lateral cortex hole or exited vascular penetrations in the femur neck. The mean volume of silicone per femur was 35 ml (range: 28–42 ml). The radiographs after elastomer filling showed a regular and reproducible pattern of silicone distribution in the head, neck and trochanteric regions of the proximal femur.

Hip Fracture Generation

Biomechanical testing was done using an LR5K*Plus* 5 kN load testing machine with a XLC-50K-A1 Load-cell and NEXYGEN*Plus* material test and data analysis software (Lloyd Instruments, Fareham Hants, UK). Fractures were generated by simulating a fall on the greater trochanter in a modified Hayes-fall configuration [24]. The femoral shaft was held firmly by a steel arm at a 20-degree angle from the horizontal plane and with the femur head 15 degrees internally rotated (Figure 1). The load was applied using a silicone-coated cup attached to the crosshead of the testing machine. The crosshead moved with 2mm/s and stopped automatically when the load cell registered an abrupt reduction in load of 75%. The recorded load was defined as fracture load (N). After each specimen was fractured plain anteroposterior radiographs were made to calculate the NSA. In case of complete displacement of the fracture the NSA was defined as 180 degrees. The type of generated fracture was classified according to the AO-classification.

Osteosynthesis

Simple and multifragmentary pertrochanteric (AO-A1 and AO-A2) fractures were treated with a dynamic hip screw (DHS) with a 4 hole plate and intertrochanteric (AO-A3) fractures were treated with a proximal femoral nail-antirotation (PFNA small, Synthes, Zuchwil Switzerland, length 200mm) following AO guidelines. The collum screws of both the DHS and the PFNA were placed with a maximum tip apex distance of 25mm, as noted in the study of Baumgaertner et al. [25]. During the osteosynthesis procedures, the operative time (min) and any technical difficulties during the procedure were recorded.

Failure Load Following Osteosynthesis

After osteosynthesis, each specimen was replaced in the load-testing machine in the same single leg stance configuration (Fig. 1).

The actuator moved with a speed of 2 mm/s and stopped when an abrupt reduction in load of 75% was detected. The recorded load was defined as failure load

(N). X-rays of all three stages, fracture after EF- osteosynthesis after EF with fracture-after failure of osteosynthesis, are shown in figure 2.

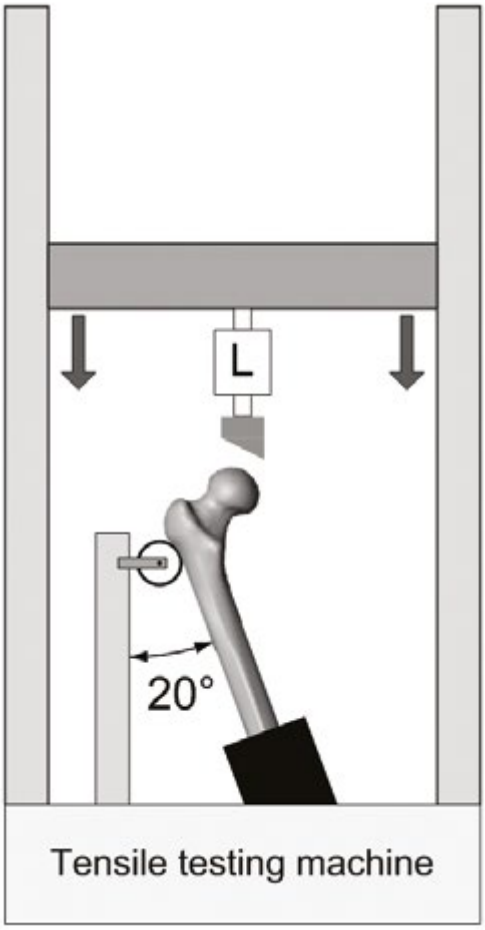

Figure 1. Graphic display of the single leg stance configuration, with the femur fixed upright at a 20˚ angle from the vertical plane and 15˚ endorotation. The 'L' marks the load cell.

Statistical Analysis

Statistical analysis was done using SPSS (SPSS 16.0, SPSS Inc., Chicago, IL, USA). Within the control and EF-group, proximal femurs were grouped according to implant used for osteosynthesis and descriptive statistics including mean and standard deviation were used. In addition, unpaired Student-T tests were performed to detect significant differences in operative time and failure load between the EF-group (n=10) and the control group (n=10). *P*-values were considered significant when <0.05.

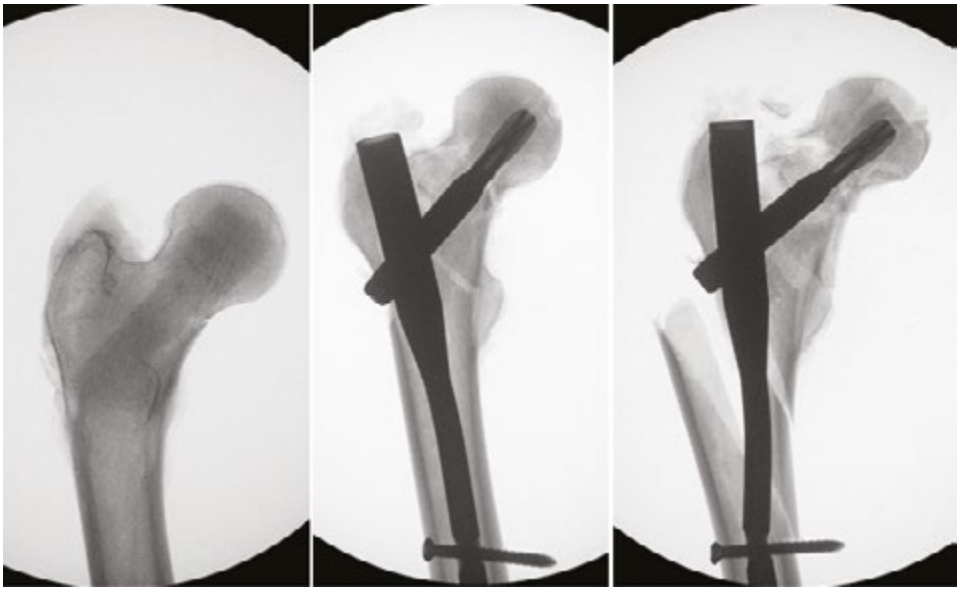

Figure 2. X-rays of the cadaveric femurs with (from left to right) Fracture after EF; osteosynthesis after EF with fracture; after failure of osteosynthesis.

RESULTS

After loading in both groups five fractures were pertrochanteric and five were intertrochanteric. In both the control-group and the EF-group, five out of ten osteosynthesis procedures were performed with a DHS and five out of ten procedures were performed with a PFNA (Table 1).

The overall mean (± SD) time to perform osteosynthesis was 20 (± 6) min in the control-group and 19 (± 5) min in the EF-group. During osteosynthesis of the fractured hip in the EF-group, no difficulties including the need for additional instruments to remove elastomer from the proximal femur were recorded.

After osteosynthesis of the fractured hip no difference in overall mean failure load was recorded between the control-group and the EF-group (3783 ± 527 N and 3472 ± 754 N, respectively) (Table 2).

DISCUSSION

The feasibility of performing standard osteosynthesis of a fractured proximal femur after preventive elastomer femoroplasty (EF) was evaluated in an in-vitro biomechanical study. We found no statistically significant differences in either operative time to perform osteosynthesis or postoperative energy-to-failure load between fractured human cadaveric femurs that were beforehand treated with EF and fractured proximal femurs without the elastomer stabilization. In addition, no technical difficulties or the need for

Table 1. Time (minutes) required to perform osteosynthesis of the proximal femur in the control-group and the elastomer femoroplasty (EF)-group, stratified by type of implant used. DHS, dynamic hip screw; PFNA, proximal femoral nail-antirotation.

Femur	Control-group		EF-group		Unpaired Student t-test
	Implant	*Min*	*Implant*	*Min*	
#1	DHS	14	DHS	16	
#2	DHS	13	DHS	13	
#3	DHS	18	DHS	17	
#4	DHS	14	DHS	13	
#5	DHS	13	DHS	12	
Mean (SD)		**14 (2)**		**14 (2)**	***P*= 0.8852**
#6	PFNA	28	PFNA	23	
#7	PFNA	22	PFNA	24	
#8	PFNA	28	PFNA	19	
#9	PFNA	29	PFNA	22	
#10	PFNA	20	PFNA	27	
Mean (SD)		**25 (4)**		**23 (3)**	***P*= 0.3171**

Table 2. Failure load (N) after osteosynthesis of the proximal femurs in the control-group and the elastomer femoroplasty (EF)-group, with either proximal femoral nail-antirotation (PFNA) or dynamic hip screw (DHS).

Femur	Control-group		EF-group		Unpaired Student t-test
	Implant	*Failure load (N)*	*Implant*	*Failure load (N)*	
#1	DHS	4510	DHS	3050	
#2	DHS	3750	DHS	2450	
#3	DHS	3200	DHS	5000	
#4	DHS	3930	DHS	2670	
#5	DHS	3200	DHS	3560	
Mean (SD)		**3718 (550)**		**3346 (1016)**	***P*= 0.4920**
#6	PFNA	3200	PFNA	4050	
#7	PFNA	3680	PFNA	3940	
#8	PFNA	4740	PFNA	2900	
#9	PFNA	3820	PFNA	3640	
#10	PFNA	3800	PFNA	3460	
Mean (SD)		**3848 (558)**		**3598 (455)**	***P*= 0.5717**

specific instrumentation to remove the elastomer was necessary for osteosynthesis of the fracture in the EF group.

This feasibility study has certain limitations. We did not compare the performance of osteosynthesis in fractured hips augmented with elastomer with osteosynthesis in fractured hips reinforced with bone cement. The concept of femoroplasty with polymethyl-methacrylate (i.e. bone cement) as a prophylactic reinforcement of the femur has been introduced previously [14, 15]. Heini et al. injected cement into osteoporotic cadaveric proximal femurs [15]. By doing so, peak fracture load for a simulated fall on the hip was increased by 82%, with a corresponding increase in energy absorption of up to +188%, compared to noninjected femurs, indicating that cement

augmentation might prevent hip fractures in elderly patients. Unfortunately, cement augmentation was associated with significant heat generation due to polymethylmethacrylate polymerisation. In addition, osteosynthesis of fractured femurs that were beforehand reinforced with cement was a challenging procedure, with particular difficulty recorded in the removal of the composite [13].

As an alternative to bone cement to reinforce the proximal femur, we introduced femoroplasty using polydimethylsiloxane [18], an elastomer that cures without exothermic heat [22, 23]. The resultant construct stability of femoroplasty with elastomer is different from that with bone cement. Unlike cement augmented femurs, peak fracture load for a simulated fall on the hip in elastomer augmented femurs was not significantly different from untreated control femurs [18]. Dislocation according to Neck Shaft Angle was significantly reduced in the EF group [18, 19]. Furthermore, during subsequent cyclic loading, the failure load of fractured femurs stabilized by EF was 2709 N [20] - well exceeding the peak loads of approximately 1500 – 2025 N during normal gait in a 75 kg individual [26, 27]. These findings suggested that EF might both reduce initial displacement of hip fractures at the time of injury as well as reduce secondary displacement rates during subsequent conservative treatment of undisplaced hip fractures. In contrast to the data available on cement femoroplasty, we found in the present study that - if surgical stabilization was necessary after all, i.e. in the event of secondary dislocation - osteosynthesis of fractured femurs that were preventively treated with EF is not associated with any additional challenges.

In this cadaveric study, we did not evaluate the presence of debris and its potential biological response elicited after osteosynthesis in EF treated hips. Elastomer is already widely used in-vivo, e.g. for the augmentation of nasal bones and in vascular grafts, because of its physiological inert properties [28-30]. These studies did not show any biological response. However, the biocompatibility of elastomer with the unique environment of cortical and cancellous bone and the marrow space is unknown. In addition, EF remains an invasive technique with possible complications including emboli, infection and hematoma. Future studies will have to investigate the in-vivo behavior of elastomer in fractured hips and subsequent osteosynthesis, and evaluate the cost-benefits of the intervention. An additional limitation of this study was that, similar to our previous experiments, we used fixed specimens instead of fresh frozen cadaveric bones. We justified this choice of material because contralateral side femurs were used for the control group.

There was a large variability in failure loads after osteosynthesis in the control-group and the EF-group (Table 3). A possible explanation for this large spread in failure loads could be the differences in hip geometry between individual proximal femora. Previous studies using cadaveric materials also found large standard deviations in the load to fracture [15, 18]. Finally, the study sample was relatively small and more cadavers would be needed to reduce the chance of a possible type II error. However,

in the present feasibility study no clinically significant difficulties in performing osteosynthesis after stabilization with EF were encountered.

In conclusion, duration of surgery, difficulty in performing the osteosynthesis, and failure load after osteosynthesis of fractured proximal femurs that were stabilized with EF were comparable to the untreated contralateral femurs. This indicates that fixation with routine osteosynthesis of secondary displaced cadaveric hip fractures is not hindered by the presence of preventive EF.

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CHAPTER 9

Thrombogenicity of a new injectable biocompatible elastomer for aneurysm exclusion, compared to expanded polytetrafluoroethylene in a human ex vivo model

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ABSTRACT

Objectives

Customized Aortic Repair (CAR) is a new concept for endovascular aortic aneurysm repair in which a non-polymerised elastomer is injected to fill the aneurysm sac around a balloon catheter. Amongst other variables, the thrombogenicity of the elastomer should be tested, before further clinical experiments can take place. The aim of this human *ex vivo* study was to measure the thrombogenicity of the elastomer and to compare it to expanded polytetrafluoroethylene (ePTFE).

Design and materials

In a validated *ex vivo* model, non-anticoagulated blood was drawn from the antecubital veins of 10 healthy donors with a 19-gauge needle. It was drawn through elastomer tubes and through ePTFE Gore-Tex vascular grafts, both 60 cm long and with an inner diameter of 3 mm.

Methods

Fibrinopeptide A (FPA) and P-selectin expression was measured in blood samples, collected at the end of the grafts. After the experiments, the deposition of platelets and fibrin onto the grafts was visualized by scanning electron microscopy.

Results

For these graft types, a progressive increase in FPA production was observed in time. No significant difference was observed between the elastomer and ePTFE grafts ($p > 0.05$). No increase in P-selectin expression, and thereby no platelet activation, was observed in the perfusate of either grafts ($p > 0.05$). By scanning electron microscopy, numerous platelet aggregates were observed on the ePTFE grafts, whereas just a few adhered platelets and no aggregates were observed in the elastomer grafts.

Conclusions

The elastomer in its current formulation has a low thrombogenicity, comparable to ePTFE, making it an ideal substance for endovascular aneurysm sac filling. Further research should clarify the feasibility of CAR *in vivo*.

INTRODUCTION

Endovascular aneurysm repair (EVAR) of abdominal aortic and other arterial aneurysms has become a well-established treatment modality [1, 2]. However, there are still several drawbacks to EVAR. Endoleaks, endotension, stent migration and stent failure are complications that might lead to re-interventions, prolonged follow-up or even rupture after treatment [3, 4]. Furthermore, EVAR has anatomical restrictions. In the literature, up to 27% of aneurysms are considered to be unsuitable for EVAR because of insufficient neck length, large neck diameter or severe angulation [5].

To overcome these anatomical disadvantages, Customized Aortic Repair (CAR, a concept formerly known as Aortic Customize) was developed as a new approach for aneurysm repair (Fig. 1) [6-8].

With this concept, the lumen of the aneurysm is excluded by one or more endovascular balloon(s), and a non-polymerized liquid elastomeric solution (polydimethylsiloxane, PDMS) is used to fill the aneurysm sac around the balloon catheter. After the *in situ* polymerization and balloon deflation, an endoluminal mould with a patent lumen excludes the aneurysm sac.

One of the key attributes of this newly engineered elastomer is its low viscosity, enabling injection into the aneurysm sac through small profile (7Fr) endovascular catheters, resulting in a fully percutaneous, rapid and easily accessible technique. Filling the cavity of the aneurysm sac with an injectable biocompatible elastomer reduces wall stress and thereby will probably reduce the chance of rupture risk, as aneurysm rupture occurs when the local wall stress exceeds the local wall strength [6, 9, 10]. Extensive *in vitro* and preliminary *in vivo* porcine experiments have shown the feasibility and potential of CAR [6, 7, 11]. The elastomer has the physical properties necessary for endovascular injection and successful aneurysm exclusion.

The direct contact with blood requires a low thrombogenicity of the elastomer to prevent occlusive thrombosis or embolization. Regular PDMS has proven its low thrombogenic properties in the past when compared to expanded polytetrafluoroethylene (ePTFE) [12]. The elastomer used in CAR is very similar to regular PDMS. However, there are no data available on the thrombogenicity of this particular elastomer. In advance of any *in vivo* animal experiments or human clinical procedures, further basic research on the thrombogenicity must be performed.

The aim of this human *ex vivo* study was to measure the thrombogenicity of the elastomer in healthy young volunteers and compare it to the thrombogenicity of ePTFE grafts, one of the most used materials in synthetic arterial grafts for aneurysm repair and peripheral bypasses.

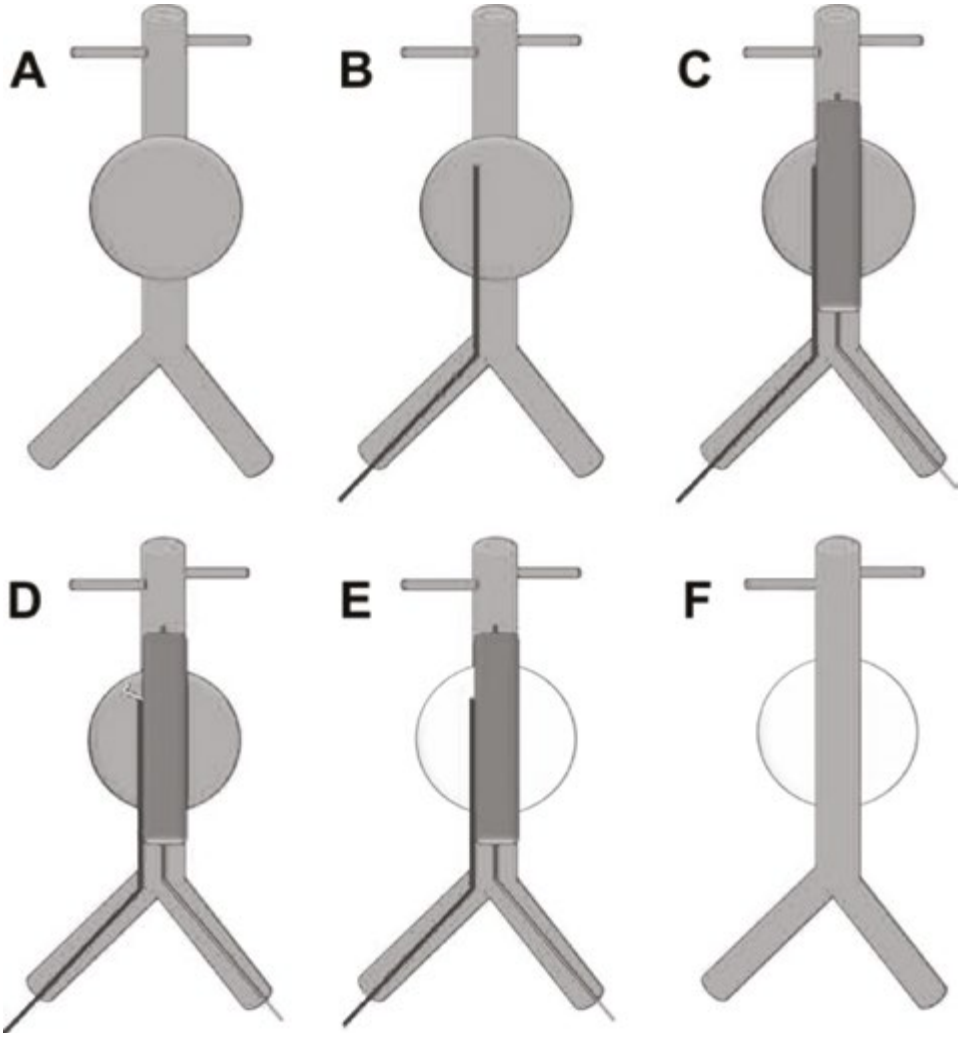

Figure 1. Customized Aneurysm Repair, the treatment concept: A. A schematic drawing of an abdominal aortic aneurysm. B. A fill catheter is inserted through a femoral artery. C. An endovacular balloon excludes the aneurysm from the circulation. D. The two components of the elastomer are pumped in the excluded aneurysm. Excess blood is pushed out alongside the balloon. E. After the aneurysm is filled, the elastomer takes 5 min to cure. F. When the elastomer has cured, the endovascular balloon is deflated, leaving the aneurysm excluded with a new lumen. Reproduced with permission from Bosnian et al. EJVES 2010;40:65-70.

MATERIAL AND METHODS

Ex vivo model

In a validated and earlier described *ex vivo* model, non-anticoagulated blood was drawn from the antecubital veins of 10 healthy donors with a 19-gauge needle (Fig. 2) [13].

A vascular graft with a length of 60 cm and a diameter of 3 mm was connected to the needle. Using a syringe pump, blood was aspirated with a constant flow rate of 20 ml min^{-1}, for 6 min. The combination of this diameter and flow rate resulted in a shear rate of 74 s^{-1}, which reflects venous flow conditions and favours fibrin-rich clot formation. A cuff was wrapped around the upper arm to ensure a constant pressure of 45 mmHg, resulting in a continuous blood flow through the graft during the experiment.

All volunteers were healthy male subjects, who had no vascular history and had no coagulopathy. The median age of the volunteers was 24.3 (range: 22—26) years. They denied taking any medication 2 weeks before the experiment and gave informed consent. The experiments were approved by the local medical ethics committee (UMCU, Utrecht, the Netherlands). Every volunteer served as his own control. Randomization of the grafts for first and second run took place. When the elastomer graft was used for the first run, the ePTFE graft was used for the second run. This second run was performed within half an hour after the first run and blood was drawn from the contralateral arm.

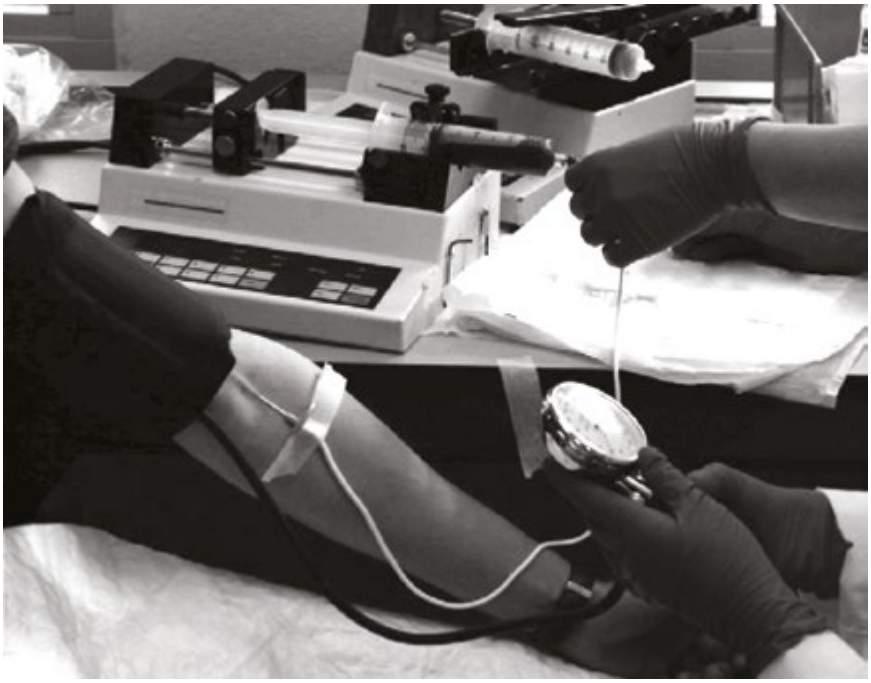

Figure 2. *Ex vivo* perfusion model using a cuff at a constant pressure of 45 mmHg to ensure blood flow. Blood is aspirated through the graft with a constant flow of 20 mL/ min, resulting in a shear rate of 74/s.

Grafts

The elastomer tubes were cast using a custom-made mould (Department of Fine Mechanics, Leiden University Medical Center, Leiden, the Netherlands). The elastomer

was a two-component room-temperature addition-cure liquid silicone formulation, obtained from Viazym BV (ViaZym BV; Delft, the Netherlands) [8]. The two components consisted of:

1. A platinum-containing vinyl-terminated PDMS, surface-treated amorphous silica and vinyl Q,
2. A methylhydro-dimethyl-siloxane copolymer containing vinyl-terminated PDMS, surface-treated amorphous silica and vinyl Q,

The two components of the elastomer were mixed using a static mixer and injected in the mould; creating solid elastomer tubes 60 cm long with an inner diameter of 3 mm. Standard ePTFE Gore-Tex vascular grafts (Gore, Flagstaff, AZ, USA) with an internal diameter of 3 mm and a length of 60 cm were used for comparison.

Blood samples and assays

Blood samples (900 µl) were collected at the end of the graft, starting directly after connection to the vein and thereafter every minute for a total of 4 min. After 4 min, samples were collected every 30 s until the end of the perfusion (total perfusion time was 6 min for each arm). The samples were mixed immediately with 100 µl of 0.5 M ethylenediamine tetra acetic acid (EDTA) and centrifuged at 3500 rpm for 5 min, and aliquots of plasma were stored at -20 °C until assayed.

Fibrinopeptide A (FPA) and P-selectin levels were determined in the blood samples. FPA is the product from the transformation of fibrinogen in fibrin, which is a process activated by thrombin release. P-selectin is a cell-adhesion molecule on the surfaces of activated endothelial cells, that line the inner surface of blood vessels, and activated platelets. When endothelial cells are activated by molecules such as thrombin or histamine during injury or inflammation, P-selectin moves from an internal cell location to the endothelial cell surface. Therefore FPA- and P-selectin-positive platelets are an adequate method to measure the advance of the activated coagulation process.

For the FPA measurements, a commercially available enzyme-linked immunosorbent assay was used as an indicator of fibrin formation (Zymutest FPA; Hyphen Biomed, Andresy, France). P-selectin expression on perfused platelets, as an indicator of activation of platelets, was determined in EDTA anti-coagulated whole blood before plasma centrifugation. Platelet activation was assayed by flow cytometric analysis using a phycoerythrin (PE)-conjugated monoclonal antibody, following the instructions for use of the manufacturer (BD Pharmingen, San Diego, CA, USA, Catalog No 555524).

Scanning electron microscopy

The deposition of platelets and fibrin onto the grafts was visualized by scanning electron microscopy. The distal end of the graft was cut into small pieces (5x5 mm), fixed in 2%

glutaral-dehyde, and then dehydrated through increasing concentrations of ethanol (80—100%). The samples were dried with the use of hex-amethyldisilazane. Next, the graft pieces were sputter-coated with a thin layer of platinum/palladium and analyzed with scanning electron microscopy (Philips XL30; Eindhoven, the Netherlands).

Statistical analysis

The results were analyzed with a paired *t* test, as implemented in the statistics program Statistical Package for the Social Sciences (SPSS) 16.0 for Windows (SPSS Inc., Chicago, IL, USA). The results were expressed as the mean ± standard error of the mean (SEM). A P value < 0.05 was considered significant.

RESULTS

In the current *ex vivo* model, non-anticoagulated blood was drawn directly from the antecubital veins over either Gore-Tex® ePTFE grafts or elastomer grafts (Fig. 2). All 10 perfusions were performed without any technical or subject-related complications.

FPA concentration was measured in plasma samples taken at different time points. For both graft types, a progressive increase in FPA production was observed in time. No significant difference ($P > 0.05$) was observed between elastomer and ePTFE grafts (Fig. 3, Table 1).

The activation of platelets during blood drawing was analyzed by measuring the percentage of P-selectin-positive platelets. No increase ($P > 0.05$), and thereby no platelet activation, was observed in the perfusate of either graft (Fig. 4, Table 1).

We also analyzed the results by using each volunteer as his own control, as one arm was used for an ePTFE graft and the other arm for an elastomer graft. Fig. 5 shows the mean differences (delta values) in FPA- and P-selectin levels per patient. These delta values were obtained by subtracting the ePTFE measurements from the elastomer values.

Using scanning electron microscopy, numerous platelet aggregates were observed on the ePTFE grafts whereas only a few adhered platelets and no aggregates were observed in the elastomer grafts (Fig. 6).

DISCUSSION

The measurements of FPA concentration and of P-selectin-positive platelets show that the elastomer, designed and tailored for CAR, has a low thrombogenicity. We found no statistically significant difference in thrombogenicity compared to ePTFE, one of the most used materials in synthetic arterial grafts for aneurysm repair and peripheral bypasses (Figs. 3 and 4, Table 1).

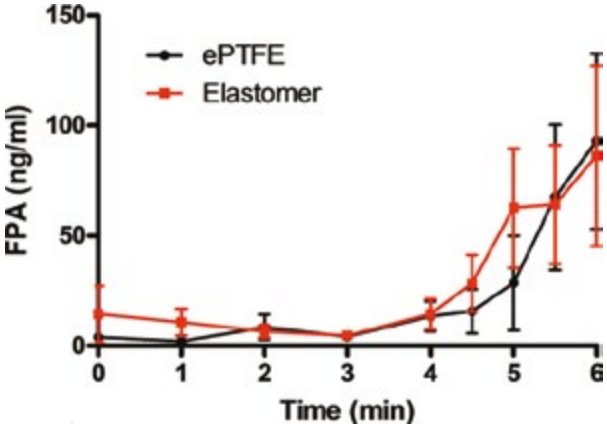

Figure 3. Fibrinopeptide A measurements show a progressive increase in fibrin formation in time during *ex vivo* perfusions. No significant differences were found between the two types of grafts. Error bars indicate standard error of the mean.

The differences in measured FPA levels and P-selectin percentages per patient were minimal as shown in Fig. 5. Individuals who had a 'strong' thrombogenic response to ePTFE also had a 'strong' thrombogenic response to the elastomer. In the same manner, individuals who had a 'moderate' response to ePTFE, had the same response to the elastomer.

The electron microscopic analysis showed a decrease in platelet adhesion and aggregation on the elastomer samples compared to ePTFE grafts (Fig. 6). Unfortunately, it was not possible to quantify these results. The extremely smooth surface of the elastomer graft compared to the porosity of the ePTFE graft could have contributed to this difference in the adhesion of platelets. As the use of ePTFE grafts in an aortic position has a low thrombosis rate, similar low thrombosis rates can be expected with the use of the elastomer.

Table 1. *P*-values of differences in FPA and P-selectin levels measured at different time points. The results were analyzed with a paired *t* test.

	FPA	P-selectin
Time (s)	*P*	*P*
0	0.72	0.44
1	0.94	0.58
2	0.88	0.74
3	0.97	0.48
4	0.90	0.53
4.5	0.33	0.68
5	0.26	0.74
5.5	0.71	0.28
6	0.66	0.60

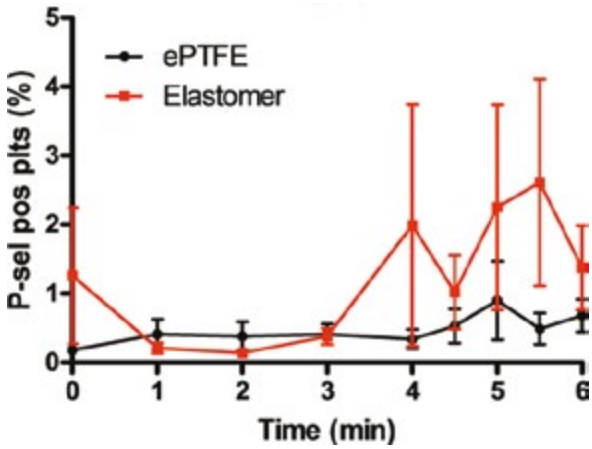

Figure 4. P-selectin expression as a measure of platelet activation during *ex vivo* perfusion. No significant increase was observed between the two types of grafts. Error bars indicate standard error of the mean.

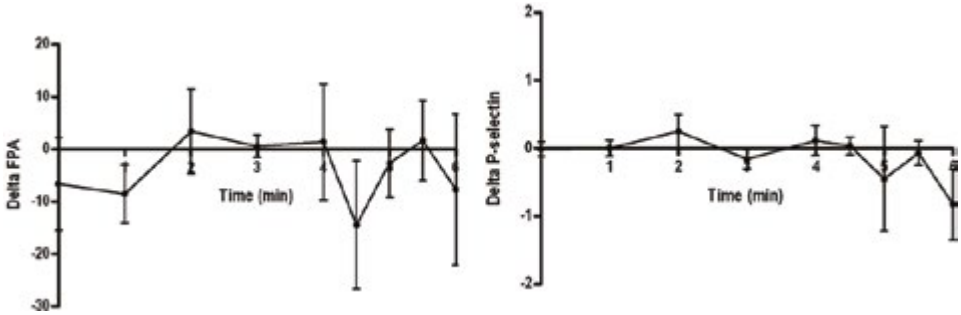

Figure 5. Graph depicting the difference in the levels of FPA and P-selectin levels in each patient (Elastomer value –ePTFE value). Error bars show SD. The delta values were obtained by subtracting the ePTFE measurement from the elastomer measurement in each patient.

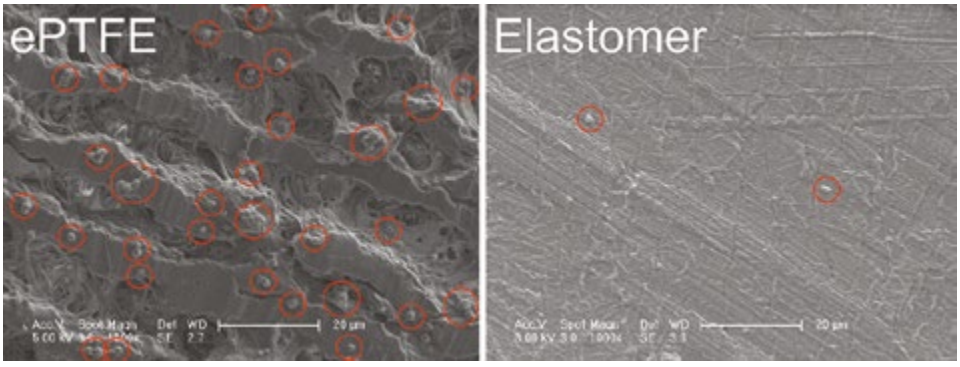

Figure 6. Scanning electron microscopy of grafts from one single donor. The circles show platelet adhesion and aggregation on the grafts after 6 minutes of perfusion with non-anticoagulated blood. On the left, the ePTFE specimen, on the right, the elastomer specimen. Pictures are representative for all healthy volunteers.

Limitations of the study

To measure the thrombogenicity of the elastomer, a previously validated human *ex vivo* set-up was used [13]. The main advantage of this *ex vivo* set-up is that the blood of the volunteer does not come in contact with surfaces other than the materials investigated. Furthermore, in this set-up, every volunteer was his own control. However, we appreciate the fact that every *ex vivo* experiment is a simplification of the complex *in vivo* situation. The small diameter (3 mm) of the grafts we used is not comparable to the diameter of the lower abdominal aorta (±19 mm). However, increased thrombogenicity and vessel occlusion is especially a problem occurring in small-diameter vessels as shear stress increases and therefore platelet activation and deposition increase. When a small, 3-mm-diameter graft shows only moderate platelet aggregation or fibrin depositions, it is likely that a wider lumen (e.g., 10—20 mm) will not show increased thrombogenicity.

Another difference with the *in vivo* situation was the average age (24.3 years) of the test subjects, while the average age of an aneurysm patient is higher (average age 60—80 years). The use of this young age group creates an unreal scenario, with regard to the thrombogenicity in the targeted patient group. A young age group was however chosen to be sure that the subjects were free of coagulopathic diseases and were not on medications that possess thrombogenic properties. For that same reason, male subjects were chosen, as they certainly do not take oral contraceptives. The high thrombogenicity in this group of young, healthy volunteers would be a major drawback of the new technique and would directly limit the use of the elastomer *in vivo*. Furthermore, the use of this age group as test subjects is a validated method in comparable thrombogenicity studies [13]. It would certainly be interesting for future experiments to repeat the experiments in a more senior age group.

A potential shortcoming of the set-up might be the hypothetical activation of the coagulation cascade when the first run of sample collection takes place. This might influence the measurements during the second run. In this study and in the earlier study with the same *ex vivo* model, no difference was shown in baseline FPA levels in both runs, indicating that systemic coagulation activation by the procedure is unlikely [13]. In addition, the randomization of the grafts used in the first and second run should have corrected for this potential bias.

Customized Aortic Repair

CAR has been developed to overcome the shortcomings of EVAR, as stated above. In an *in vitro* set-up, it has proven to significantly reduce aneurysmal wall stress [6]. When endovascular balloons become available in different forms and configurations, in theory, any aneurysm with a deviant anatomy will be treatable with endovascular techniques using elastomer sac filling.

Although new EVAR grafts (e.g., the *Endurant* and the *Aorfix)* have been launched, which prove the ability to treat severe angulations [14, 15], with many of the current EVAR techniques, severe angulations may still lead to kinking of the graft material and eventually to migration of the graft [16-18]. As no additional supporting graft material is used, these problems are not likely to occur with CAR. The fluidity of the non-polymerized elastomer inherently causes adjustment to the geometry of the aneurysm, not only by filling the large cavity of the aneurysm sac but also by diffusing into all irregularities and side holes. The elastomer mould will attach itself as it customizes itself to the form of the abdominal aorta aneurysm (AAA) sac.

Angulation and occlusive disease of the iliac arteries are an important exclusion criterion for EVAR, and tortuosity may form a serious obstacle for a successful EVAR procedure. A minimal diameter of 12—22 Fr is often needed to access the bulky and rigid delivery sheath. To fill the sac with the biocompatible elastomer, a catheter of only 7 Fr is needed. Preliminary *in vivo* porcine experiments have shown that this concept is technically feasible [7].

Besides the treatment of AAAs, CAR may prove a possible treatment modality for thoracic-aorta aneurysms, peripheral aneurysms and iliac aneurysms. With the current EVAR techniques, iliac aneurysms can sometimes be difficult to treat due to short distal sealing areas, leading to coiling and overstenting of the internal iliac artery. With the CAR concept, there is no necessity for a long landing area, and this may prevent the necessity to overstent the iliac artery, thereby preventing the introduction of buttock claudication and ischemia.

Beside the stand-alone treatment concept, the elastomer injection technique is more broadly applicable. The elastomer can already be used as an adjuvant with current stent grafts when problems of endoleak or migration occur. In these cases, the elastomer can be used to fill up the aneurysm sac and secure the endovascular stent graft [11, 19].

The CAR concept is not the only aneurysm treatment concept that addresses aneurysm cavity filling. Early *in vivo* human results with the *Nellix* have been recently published and show promising results [20]. The Nellix concept uses 'bag-filling' to fixate its 20 Fr grafts with endo-bags in the aneurysm cavity. Although it may seem very similar, it is a different concept than the concept presented in the current manuscript, as it always needs a bulky graft for aneurysm exclusion. Furthermore, the polymer is injected in a closed endo-bag instead of 'free-range', thereby limiting its 'customizing' capabilities. Nevertheless, the Nellix graft has very promising results and may prove to be an excellent addition to the abdominal aneurysm treatment modalities.

The elastomer

The elastomer used in this study was designed for aneurysm sac filling in CAR [6-8, 11]. It consists of PDMS that has a widespread use in multiple *in vivo* applications. PDMS

is a biocompatible elastomer, and grafts coated with PDMS have shown less graft stenosis compared with other grafts [12, 21-25]. The current formula is non-toxic and the product cross-links isothermally in the presence of blood, without the release of toxic by-products. Viscosity of the compound allowed infusion rates of up to 2 ml s^{-1} using a standard angiographic pump with an injection pressure up to 1200 pounds per square inch. The substance has an average polymerization time of approximately 5 min. After curing, the material had a yield stress of approximately 400 kiloPascal (kPa), failing at more than 20% elongation. The density of the cured elastomer is 1.0167 g $crrT^{3}$. More details about the development of the current elastomer can be found in an earlier publication [7].

Clinical relevance

CAR may prove to be an exciting new endovascular treatment modality to exclude different types of aneurysms. As mentioned above, the concept of aneurysm sac filling is feasible in several *in vitro* and *in vivo* set-ups [6, 7, 11, 19]. Before clinical applications can take place, the biocompatibility, biostability and the thrombogenicity have to be indisputable. The current study showed that the elastomer has, according to FPA- and P-selectin measurements (Figs. 3 and 4), a thrombogenicity comparable to ePTFE, the preferred material in synthetic (endo-)vascular grafts. The elastomer tubes seem to be superior to the ePTFE tubes with regard to adhesion of platelet aggregates (Fig. 6).

CONCLUSIONS

In conclusion, the elastomer in its current formulation has a low thrombogenicity, comparable to the thrombogenicity of ePTFE, in an *ex vivo* human model. This property makes it an ideal substance for endovascular aneurysm sac filling. Further research should clarify the thrombogenicity of the elastomer *in vivo,* as well as the feasibility of the novel treatment concept 'Customized Aortic Repair' *in vivo*.

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CHAPTER 10

General Discussion

GENERAL DISCUSSION

The aim of this thesis was to evaluate prevalence and clinical sequelae of second hip fractures in two areas in the Netherlands (part 1). Secondly, a biomechanical and biocompatibility evaluation of elastomer femoroplasty (EF), an experimental technique to prevent hip fracture surgery, was performed (part 2 and 3). The ***introduction*** and ***Part 1*** of this thesis discuss the incidence and sequelae of first and second, contralateral hip fracture and their social and economic impact. The current incidence of hip fractures and the prospected increase in the growing elderly population urgently calls for preventive measures. Over the past decades several of these preventive measures have been introduced. Programs to prevent falling by balance training [1] or marshal-arts fall techniques [2] have promising results and prospective randomized trials on fracture prevention by treating osteoporosis with bisphosphonates, vitamin D and calcium have shown their efficacy [3-6]. However since the introduction of fall and fracture prevention programs, the percentage of second hip fractures has not decreased [7, 8]. Furthermore the debate on long-term bisphosphonate use is very contemporary, since the report of data on long-term bisphosphonate-use related fractures [9, 10].

Although there is no doubt that major surgery in elderly individuals results in functional decline [11, 12], it remains unknown whether second, contralateral hip fracture surgery is associated with an additional risk of postoperative complications and discharge institutionalization. ***Chapter 3*** describes patient and fracture characteristics, the early postoperative complication rate, and the need for discharge institutionalization in seventy-one consecutive patients with a second hip fracture at the St. Elisabeth Hospital in Tilburg, the Netherlands. Significantly more postoperative complications were found after the second hip fracture compared to the first hip fracture, with close to twice the number of complications per patient after second, contralateral hip fracture surgery. In addition, the complications were more severe after second hip fracture surgery than documented after first hip fracture surgery. Only approximately one third of the patients were able to return to their own home after treatment for second hip fracture. The impact of these sequelae on the patients' life makes contralateral hip fracture prevention mandatory. Particularly when a selection of frail patients with increased risk of a second, contralateral hip fracture can be made (i.e. older age with weakened motor skills, visual impairment, dementia, respiratory disease or solitary life after first hip fracture or radiographic osteoporosis at the hip (the Singh Index). These patients will potentially benefit the most from new measures to prevent contralateral hip fracture surgery.

In ***Chapter 4*** of ***Part 2***, we present the concept and the surgical technique of elastomer femoroplasty (EF). ***Chapters 5 through 8*** discuss the biomechanical properties of femoroplasty using an elastomer in an *in vitro* cadaveric experiment. In ***Chapter 5*** we first named the technique "augmentation with silicone", analog to cement augmentation. Augmenting the strength of the proximal femur to prevent a

hip fracture with a stiff compound like bone cement (PMMA) increases the load-to-fracture of the proximal femur [13, 14]. However, in case of failure it could well lead to complex fractures below the augmented proximal femur. Fracture surgery after cement augmentation will probably be tedious and more extensive with subsequent increased morbidity and mortality [15, 16]. The main objective of EF is not to increase resistance to load of the proximal femur, in order to prevent a fracture, but to prevent dislocation of the fracture parts after hip fracture. Thus allowing primary fracture healing (i.e. conservative treatment of the fracture without surgery). That is why a more appropriate term for our technique is "elastomer femoroplasty" instead of "augmentation with silicone".

In all our biomechanical experiments human cadaveric femurs conserved in formaldehyde were used. From each pair of femurs one was randomly selected for femoroplasty and the contralateral hip served as a control. In ***Chapter 5*** we tested the load to fracture in a simulated-fall-configuration and the load to dislocation in a single-leg-stance-configuration. Load was recorded with a load cell in the tensile testing machine and dislocation after fracture was calculated using the Neck-Shaft-Angle (NSA). The conclusion of this first biomechanical experiment was that the injected elastomer did stabilize the proximal femur considering the change of NSA after loading as outcome, but it did not augment the proximal hip in a way that the load to fracture was increased. In fact there was a non-significant decrease in fracture load of approximately 10%. This decrease could well be attributed to the size of the entrance hole in the lateral cortex, analog to the increased risk of fracture when a femoral metastasis causes a cortical bone lesion [17-19]. Although the size of our entrance in the lateral cortex was only 10 mm, it remains a considerable gap especially in smaller femurs. This is confirmed by Kukla et al. who showed a decrease in load to fracture of the proximal femur by 21% after removal of a dynamic hip screw and by 41% after removal of a standard gamma-nail implant in a biomechanical cadaveric study [20]. The entrance hole in the lateral cortex could also explain the increase in trochanteric fractures in our EF cadaver group. In three of the treated femurs the fracture line passed the entrance hole in the lateral cortex.

Thus, refinement of the femoroplasty technique with a smaller entrance hole at the lateral cortex was explored. In ***Chapter 6*** two different techniques were examined. Both techniques used a 3.5 mm entrance hole in the lateral cortex. Followed by a kyphoplasty balloon expanding technique and an excentric drill (Technique A) or excentric drill alone (Technique B). The balloons and drills were used to create a channel in the femoral neck and a larger cavity in the femoral head. When the cavity was filled up with the elastomer, a dog bone like distribution of the elastomer was realized. After inducing a fracture, the elastomer kept the fracture parts together. Both techniques A and B prevented fracture dislocation. Again there was a non-significant load to fracture reduction compared to the controls in both groups. However the load

to fracture after EF now only decreased 3.5% for the kyphoplasty balloon and 6.3% for the drill technique, compared to 10% in the first experiment with the larger hole at the lateral cortex. This reduction was considered to be related to the smaller diameter of the entrance hole at the lateral cortex of the proximal femur. In vivo this 3.5 mm defect in the lateral cortex is likely to heal by bone formation within a short period of time. The balloon technique created a significantly greater cavity for the elastomer, however this did not result in significant differences in fracture loads or NSA between both groups.

The next step to assess the effect of EF in the prevention of hip fracture surgery was cyclic loading of the proximal femur-elastomer construct. In ***Chapter 7***, fractured human cadaveric femurs that were prophylactically treated with EF (in Chapter 6) were cyclically loaded, mimicking walking. The outcome variables were load to failure (i.e. full displacement) and displacement during cyclic loading. The mean failure load during cyclic loading was 2709 N. This well exceeds peak loads during normal gait in a 75 kg individual, which are approximately 1500 – 2025 N [21, 22]. After regular hip fracture surgery or hemiarthroplasty these peak loads could even be considerably lower since post-operative pain constrains the patient from full weight bearing [23]. In fact Koval et al concluded that elderly patients who were allowed to bear weight as tolerated after surgical treatment of a fracture of the femoral neck or an intertrochanteric fracture, appeared to voluntarily limit loading of the injured limb to 51% during the first post-operative week [24]. These patients have to be stimulated to walk and are prescribed pain relief medication to gradually reach 87% at 12 weeks. Comparable pain and consequent limited loading could be expected after fracture of an EF preventively stabilized hip. The above data support the assertion that these EF treated hips have a low probability of secondary displacement in case a fracture occurs.

However, in the event that EF fails to stabilize the fracture parts and secondary displacement does occur, or fracture healing is impaired in any other way, some form of osteosynthesis or hemiarthroplasty should be possible. ***Chapter 8*** reported the feasibility of osteosynthesis of cadaveric femurs after EF with either a Dynamic Hip Screw (DHS) or Pertrochanteric Femur Nail Antirotation (PFNA). Neither surgical time to perform osteosynthesis nor postoperative loads to failure were different between fractured human cadaveric femurs with or without EF. In addition, no technical difficulties occurred and no extraordinary surgical instruments were necessary during osteosynthesis in the EF-group.

In ***Chapter 9*** the biocompatibility of the elastomer is discussed. The main ingredient of the elastomer was Polydimethylsiloxane (PDMS). PDMS is used in multiple *in vivo* applications. It has been widely accepted for bone augmentation in plastic surgery because of its variability in hardness (depending on the mix of chemical components). Its ability to be easily molded and shaped, and its biological inertness [25] makes it ideal for the use in facial implants. Vascular grafts coated with PDMS have shown less graft stenosis compared to other vascular grafts [26-29].

To ensure easy injection trough small bore catheters or trocars, the elastomer we used was engineered out of two components. After mixing, the elastomer cured without exothermic heat or the release of byproducts. Although it is likely for the elastomer used in EF to have comparable biocompatibility as PDMS, tests will have to confirm its biocompatibility before clinical trails can commence. Furthermore, as stated in the introduction, the elastomer should have a low thrombogenicity in case of venous embolization or expansion of the elastomer in the extra-osseous capsular veins. The elastomer used in femoroplasty is similar to an elastomer used in experiments on Customized Aortic Repair (CAR) [30-32]. In these experiments aortic aneurysms were treated by injecting elastomer into the sac of an aneurysm. Inflated balloons warrant the vascular lumen for blood flow after curing of the elastomer. For this particular vascular application of the elastomer, low thrombogenicity was paramount. In the experiment reported in Chapter 9, a previously validated human *ex vivo* set-up was used to evaluate the thrombogenicity of our elastomer [33]. The main advantage of this *ex vivo* set-up was that the blood of the volunteer did not come in contact with surfaces other than the materials investigated. The results showed that the elastomer has, according to FPA- and P-selectin measurements, a thrombogenicity comparable to ePTFE, the preferred material in synthetic vascular grafts. The elastomer tubes appeared superior to the ePTFE tubes with regard to adhesion of platelet aggregates. This experiment confirmed the low thrombogenicity of the elastomer we used in CAR and in EF.

CONCLUSION AND FUTURE DIRECTIONS

Demographic changes will result in a tidal wave of fractures in the growing group of frail octo- and nonagenarian citizens. These osteoporotic fractures are a major burden to the patients' quality of life. They will also have a major impact on health care recourses. Despite all preventive measures, predominantly focusing on osteoporosis medication, the total number of second, contralateral hip fractures has not declined over the past decades. Complications and institutionalization after surgery for a second hip fracture are increased and can be held responsible for a decrease in quality of life for these patients and high healthcare costs. Elastomer femoroplasty is a readily available, inexpensive and minimal invasive technique. EF can be applied during ipsilateral hip fracture surgery and does not need a separate operation or anesthesia. Furthermore, due to the nature of any surgical intervention, patient compliance after EF is 100%. Finally, in case of failure of EF to prevent displacement of the fractured hip, it is easy to stabilize the fracture with routine osteosynthesis.

After hip fracture approximately 10% of patients acquire a second, contralateral hip fracture. Considering the high rate of complications and the high expenditure on costs after second hip fractures compared to the low costs of EF, treating all first hip fracture patients with a preventive minimal invasive procedure like EF would probably be cost effective. However approximately 90% of patients will be treated without ever sustaining a future second hip fracture. Thus, finding and selecting patients with the highest risk for second hip fracture through a prediction model (i.e. Markov model) will optimize the EF treatment of these patients and increase cost effectiveness.

We made a major step towards CE marking of the elastomer by proving its low thrombogenicity, however further biocompatibility tests will have to be done. Animal experiments to determine the effect of EF on bone vasculature and possible side effects of intra-osseous injection could be an important next challenge. Finally, Roentgen Stereophotogrammetric Analysis (RSA) can be used for the biomechanical in vivo testing of the primary bone healing after fracture in EF treated bones. RSA can measure fracture displacement in three dimensions in up to 0.1mm and 0.1 degree [34-36]. These tests can be part of a phased introduction of new medical technologies in order to provide optimal patient safety [37].

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CHAPTER 11

Summary

SUMMARY

Part 1. Sequelae of second hip fracture surgery

Chapter 1 introduces the problem of first and second, contralateral hip fractures. The expected growth in incidence of hip fractures in the Netherlands and worldwide, as a result of demographic changes is presented. An overview of the current preventive modalities aimed at both fall, and fracture prevention is given. Although numerous of these preventive modalities have been introduced in the last decades, the incidence of second, contralateral hip fractures has not declined. The aim of this thesis is twofold: 1. to explore the prevalence and sequelae of second, contralateral hip fractures and 2. a biomechanical and biocompatibility evaluation of elastomer femoroplasty (EF).

The study we present in ***Chapter 2*** is a descriptive analysis of second, contralateral hip fractures. For this retrospective study, patients were selected from the database of the Leiden University Medical Centre. A total of 32 second, contrlateral hip fractures were found and analyzed. First and second hip fracture-types were identical in 75% of the patients. However only 8 out of 24 hips were treated with the same implant. There was a significant difference in Singh index between both hips at the time of the first fracture and between the unfractured hip at the time of the first hip fracture compared to itself at the time of the second fracture. We conclude from this small cohort that there is a significant effect of the radiographic osteoporosis appearance as measured with the Singh index on second proximal femur fracture occurrence.

In ***Chapter 3*** we present a retrospective study to determine early postoperative complication rate, and need for institutionalization at time of discharge from the hospital in patients treated for a second, contralateral hip fracture. During a six-year period (2003-2009) seventy-one patients (60 women and 11 men; age range 54 – 94 years) underwent first hip fracture surgery and subsequent contralateral hip fracture surgery at our hospital. Data from both hospitalization periods were compared. The early complication rate in patients sustaining a second, contralateral hip fracture was almost twice that documented after the first hip fracture. Following second hip fracture surgery, most patients resided in an institutional care facility.

Part 2. Elastomer femoroplasty.

Chapter 4 introduces elastomer femoroplasty (EF) as a new and experimental modality to prevent hip fracture surgery. Using a minimal invasive technique this new approach does not aim to prevent the hip fracture itself, but it aims to prevent dislocation after the fracture. This should enable bone healing with fracture consolidation conservatively, without surgery. In high risk patients EF can be performed during ipsilateral hip fracture surgery. A detailed description of the technique is presented in this chapter.

In ***Chapter 5*** we describe our first in vivo biomechanical experiment with EF using human cadaver femurs. We randomly assigned 10 paired cadaver femurs for elastomer femoroplasty and biomechanically tested for fracture load and dislocation against their native contralateral control. A load-testing machine was used for fracture induction. All femurs were first fractured in a simulated fall configuration followed by dislocation in a "single-leg-stance" configuration. Dislocation was assessed using the AO-classification and measuring the Neck-Shaft-Angle's (NSA). All treated femurs showed complete reposition according to NSA after dislocation versus only two of the controls ($P< 0.001$). Unfortunately fracture loads were approximately 10% lower in the treated group ($P= 0.304$). We held the 10 mm entrance hole in the lateral cortex accountable for this non-significant difference.

In ***Chapter 6*** we address the above-mentioned possible adverse effect of the large entrance hole. Two different minimal invasive EF techniques were designed and we compared femur strength and the ability to prevent dislocation of both techniques. A total of sixteen fixed human cadaveric femur pairs were used. From each pair one femur was randomly assigned for EF. In these femurs we drilled a 3.5 mm entrance in the lateral cortex. Cavities for the elastomer were created by: group A, balloon and group B an excentric drill. All femurs were fractured by simulating a fall on the greater trochanter. Neck-Shaft-Angles on plain anterior posterior radiographs were measured to determine fracture displacement. The results of this study show that minimal invasive EF prevents fracture displacement of the proximal femur. The compromise in load-to-fracture was now less striking, 3.5% for the balloon and 6.3% for the drill technique, compared to the 10% drop in our previous experiment. We contributed this improvement to the smaller diameter of the entrance hole.

The aim of the study presented in ***Chapter 7*** was to establish the failure loads and interfragmentary movement of fractured, elastomer femoroplasty treated femurs during cyclic loading. Sixteen cadaveric femurs were treated with elastomer femoroplasty and fractured in a simulated fall configuration. Each specimen underwent 10 cycles with a preload of 50 Newton (N), starting with a peak load of 250 N followed by 10 cycles of 500N and continued with 500N increments. The crosshead speed of the testing machine was 2 mm/s. The failure load, the number of completed cycles, and crosshead extensions were recorded. The mean failure load was 2709 N (SD 1094). At 1500 N (two times the bodyweight of a 75 kg individual) the movement of fracture parts was 3.16 mm. Preventive EF leads to stabilization of the proximal femur after fracture. In a single leg stance configuration, cyclic loading with mean failure loads that well exceed the peak loads during normal gait is feasible.

In ***Chapter 8*** we describe the feasibility of performing osteosynthesis of a fractured hip that has been treated with EF in the event that secondary displacement does occur.

Ten pairs of human cadaveric femurs were fractured in a simulated fall configuration. From each pair, one femur was randomly selected for EF prior to fracture generation and the contralateral femur was used as control. Following hip fracture generation, osteosynthesis was performed in all femurs and the operative time, technical difficulties during the procedure, and postoperative failure-load were recorded. We found that fixation with routine osteosynthesis of displaced cadaveric hip fractures is not hindered by the presence of previously injected elastomer.

Chapter 9 describes an experiment to determine the thrombogenicity of the elastomer that we used both in EF and in Customized Aortic Repair (CAR). CAR is a new and experimental concept for endovascular aortic aneurysm repair in which a non-polymerized elastomer is injected to fill the aneurysm sac around a balloon catheter. An important part of the biocompatibility of the elastomer is the evaluation of its thrombogenicity before further clinical experiments of CAR and EF can take place. The aim of this human *ex vivo* study was to measure the thrombogenicity of the elastomer and to compare it to expanded polytetrafluoroethylene (ePTFE) the gold standard for prosthesis material in vascular surgery. We used a validated *ex vivo* model, in witch non-anticoagulated blood was drawn from the antecubital veins of 10 healthy donors with a 19-gauge needle. It was drawn through elastomer tubes and through ePTFE Gore-Tex vascular grafts, both 60 cm long and with an inner diameter of 3 mm. Fibrinopeptide A (FPA) and P-selectin expression was measured in blood samples, collected at the end of the grafts. After the experiments, the deposition of platelets and fibrin onto the grafts was visualized by scanning electron microscopy. We found no significant difference in thrombogenicity between the elastomer and ePTFE grafts. By scanning electron microscopy, numerous platelet aggregates were observed on the ePTFE grafts, whereas just a few adhered platelets and no aggregates were observed in the elastomer grafts. We concluded that the elastomer in its current formulation has a low thrombogenicity, comparable to ePTFE, making it an ideal substance for endovascular aneurysm sac filling and save to use in Elastomer Femoroplasty.

CHAPTER 12

Nederlandse Samenvatting

Summary in Dutch

SAMENVATTING

In ***Hoofdstuk 1*** van dit proefschrift wordt ter inleiding een overzicht gegeven van de prevalentie en de gevolgen van eerste en tweede (contralaterale) heupfracturen. Daarnaast worden in dit hoofdstuk hedendaagse fractuur preventie strategieën besproken en het povere effect daarvan op de incidentie van tweede heupfracturen.

In Nederland worden jaarlijks ruim 19.000 patiënten opgenomen met een heupfractuur. De verwachting is dat dit aantal in de toekomst fors zal toenemen als gevolg van demografische veranderingen, met een geschatte wereldwijde prevalentie van 6.3 miljoen heupfracturen in het jaar 2050. Eén derde (32%) van de patiënten met een heupfractuur overlijdt binnen een jaar, het merendeel hiervan overlijdt in de eerste 3 maanden. Van de patiënten die wel overleven na een heupfractuur keert de helft nooit meer terug tot het niveau van functioneren van vóór de fractuur; 25% van deze patiënten verblijft een jaar nadat zij een heupfractuur opliepen nog in een instelling voor langdurige zorg, een zeer grote immateriële schade. Het verlies van kwaliteit van leven voor deze patiënten en de gevolgen voor hun omgeving zijn aanzienlijk. Daarnaast is de behandeling van een heupfractuur ook een dure aangelegenheid. Jaarlijks wordt aan de ziekenhuisopnamen van heupfractuurpatiënten ongeveer 500 miljoen euro besteed. De financiële gevolgen van het verlies van onafhankelijkheid zijn nog vele malen groter.

De omvang en de ernst van het probleem vragen om een preventieve aanpak. Tot op heden is deze preventieve aanpak gericht op (1) het voorkomen van de val en (2) het voorkomen van een fractuur na de val. Valpreventie en balanstraining hebben weliswaar een positief effect op het voorkomen van osteoporotische fracturen, maar zijn alleen van toepassing op een kleine groep vitale patiënten. Fractuurpreventie door medicamenteuze osteoporose behandeling is bewezen effectief in onderzoeksetting. Landelijke programma's om alle patiënten met een osteoporotische fractuur te behandelen zijn niet of onvoldoende ingevoerd. Er is dus een grote kans op onderbehandeling van de osteoporose na een heupfractuur. Daar boven op komt nog de matige therapietrouw van medicamenteuze osteoporose behandeling. Andere alternatieven zoals de *hip-protector* (onderbroeken met kussens ter hoogte van de heup) en zachte vloeren in verpleeghuizen, zijn inmiddels onderzocht en niet effectief bevonden. Deze preventieve maatregelen hebben dan ook geen effect op de incidentie van heupfracturen gehad. Ook het percentage tweede heupfracturen is al decennia stabiel. Tien tot 16 procent van de ruim 19.000 heupfracturen is een tweede, contralaterale, heupfractuur. De beperkte gegevens over de gevolgen van deze tweede heupfracturen wijzen uit dat patiënten meer postoperatieve morbiditeit hebben, meer invaliditeit en een groter verlies van onafhankelijke mobiliteit.

In tegenstelling tot val- en fractuurpreventie, is elastomer femoroplasty (EF) gericht op de preventie van fractuurdislocatie. Na een heupfractuur voorkomt de preventief verrichtte EF dat er dislocatie in de fractuurdelen ontstaat. De

heupfractuur kan nu conservatief, dus zonder chirurgie, behandeld worden zoals bij een succesvolle behandeling van een geïnclaveerde fractuur. De morbiditeit van operatie en ziekenhuisopname blijft de patiënt dan bespaard. Omdat de voorgestelde behandeling op zichzelf een extra, zij het minimaal invasieve, operatie is, ligt het voor de hand om ons eerst te richten op de preventie van die tweede heupfracturen. Tijdens de heupfractuurchirurgie aan de ipsilaterale zijde kan dan de contralaterale heup preventief behandeld worden met EF.

Het onderzoek in dit proefschrift brengt de prevalentie en de gevolgen van tweede heupfracturen in kaart (deel 1). Daarnaast is de preventie van heupfractuur chirurgie door middel van elastomeer femoroplasty (EF) getest in biomechanische en biocompatibiliteit studies (deel 2 en 3).

Deel 1. Sequelae van tweede heupfractuur chirurgie

Het verschil in fractuurtype tussen de eerste en tweede heupfractuur en ook het verschil in de behandeling wordt uiteengezet in ***Hoofdstuk 2***. In het Leids Universitair Medisch Centrum (LUMC) werden de medische dossiers van 32 patiënten met een tweede heupfractuur geanalyseerd. Bij 75% van deze patiënten was het type van de eerste heupfractuur gelijk aan dat van de contralaterale heupfractuur. De keuze van het implantaat voor de behandeling van de twee fracturen was slechts in een derde van deze identieke heupfracturen gelijk. Het lijkt waarschijnlijk dat de voorkeur van de operateur en de ervaring met het implantaat doorslaggevend zijn voor de keuze. Verder wordt in dit hoofdstuk de Singh Index (een eenvoudige meting van de botbalkjes op de röntgenfoto van de heup) gebruikt om osteoporose vast te stellen. We zien een significante verslechtering van de Singh index tussen de eerste en tweede heup fractuur, wat pleit voor direct preventieve behandeling na eerste heupfracturen.

In ***Hoofdstuk 3*** wordt de impact van een tweede heupfractuur op de postoperatieve morbiditeit en institutionalisering beschreven. In het St. Elisabeth Ziekenhuis in Tilburg werden over een periode van 6 jaar, 920 patiënten opgenomen met een heupfractuur. Uit deze groep werden 71 patiënten (8%) geopereerd aan een contralaterale heupfractuur. Bijna de helft (46%) van deze tweede heupfracturen vond plaats binnen 2 jaar na de eerste heupfractuur. Na een tweede heupfractuur zagen we het aantal patiënten met postoperatieve complicaties bijna verdubbelen. Het merendeel van de patiënten verloor na een tweede heupfractuur zijn onafhankelijke mobiliteit en werd ontslagen naar een verpleeghuis.

Deel 2. Elastomer Femoroplasty

Het concept van elastomer femoroplasty (EF) wordt uitgelegd in ***Hoofdstuk 4***. Via een minimaal invasieve, percutane techniek wordt een entree gemaakt in het proximale femur. Daarna wordt er ruimte gemaakt in de kop en de hals van het heupbot met een

excentrisch boor en/of met een ballontechniek. Hierna wordt een vloeibaar elastomeer ingespoten. Dit elastomeer hardt dan in enkele minuten uit tot een flexibele stent in het proximale femur**.** Het uitharden vindt bij lichaamstemperatuur plaats, zonder verdere temperatuurstijging of vrijkomen van bijproducten.

Preventieve EF is niet bedoeld om de heupfractuur zelf te voorkomen, maar om verplaatsing in de fractuurdelen na een fractuur te minimaliseren. Deze niet-verplaatste heupfractuur kan dan genezen zonder dat operatieve fixatie van de fractuurdelen nodig is. In de praktijk zal een patiënt die geopereerd moet worden voor een eerste heupfractuur, direct preventief behandeld kunnen worden aan de contralaterale kant. Gezien het minimaal invasieve karakter van EF en de veronderstelde biocompatibiliteit van het elastomeer is te verwachten dat EF aan de contralaterale zijde, minimaal additioneel operatierisico met zich meebrengt ten opzichte van het aanzienlijke risico van de heupfractuurchirurgie aan de ipsilaterale zijde.

In ***Hoofdstuk 5*** wordt het in vitro biomechanische experiment met EF beschreven. Voor dit onderzoek werden 10 gepaarde kadaverbotten gebruikt. Van elk paar werd een femur voor EF behandeling gerandomiseerd, het andere femur diende als controle. Vervolgens werden de botten gebroken in een gestandaardiseerde val-opstelling. Daarna werd de "Neck-Shaft-Angle (NSA)", dat is de hoek tussen de nek en de schacht van het femur, gemeten als uitkomstmaat voor dislocatie. Hoe meer de hoek afwijkt van de hoek die vóór de fractuur gemeten werd, hoe groter de mate van dislocatie. Tenslotte werden de botten geplaatst in een opstelling die belasting simuleert van staan op één been. De kracht die nodig was om de fractuur te disloceren werd gemeten. Hierna werd opnieuw gekeken naar de NSA. De resultaten van deze NSA metingen tonen een significante reductie in fractuur-dislocatie in de met EF behandelde botten, zowel na fractuur generatie als na belasting op één been. In de breekproeven zagen we ook dat de behandelde botten ongeveer 10% minder belast konden worden ten opzichte van de onbehandelde controles. Deze daling in piekbelasting hebben we toegeschreven aan de 10 mm grootte entree in de laterale cortex van de heup waardoor de EF is verricht.

De daling in de belastbaarheid ten gevolge van het 10mm entree bij de EF behandelde botten was aanleiding voor het in ***Hoofdstuk 6*** beschreven experiment. Het doel was om de entree in de laterale cortex zo klein mogelijk te maken waardoor de belasting tot aan het ontstaan van een fractuur minder zou dalen ten opzichte van de controles. Hiervoor zijn 2 technieken bedacht die beiden door een entree van 3.5 mm in de laterale cortex uitgevoerd werden. Opnieuw werd gekozen voor gepaarde kadaverbotten (N=16), die binnen elk paar gerandomiseerd werden voor behandeling met techniek A of B versus een onbehandelde controle. Techniek A was het creëren van een holte voor het elastomeer met een ballon en bij techniek B werd deze holte met een excentrische boor gemaakt. Na EF werden beide groepen getest in een gestandaardiseerde val-opstelling. De belasting tot aan een fractuur en de NSA vóór

en na fractuur werden gemeten. Er was geen significant verschil in belasting tot een fractuur tussen de met techniek A of B behandelde botten en hun gepaarde controles. Er was ook geen significant verschil tussen groep A en B. De belasting tot een fractuur was in groep A gedaald met 3.5% en in groep B met 6.3% ten opzichte van de niet behandelde controle-botten. Het is aannemelijk dat deze verbetering ten opzichte van de in hoofdstuk 5 beschreven 10% het gevolg is van de kleinere entree in de laterale cortex. De mate van dislocatie voor en na fractuur gemeten met NSA, was significant beter in de EF behandelde botten; er zat geen verschil in groep A of B. Geconcludeerd wordt dat preventieve EF de dislocatie na fractuur voorkomt.

Hoofdstuk 7 beantwoordt de vraag of een patiënt met een EF voorbehandelde en daarna gefractureerde heup zou kunnen mobiliseren. EF behandelde kadaverbotten werden gebroken en daarna in een opstelling geplaatst die belasting simuleert van het staan op één been. Vervolgens werden de heupen met oplopende krachten belast. Steeds werden 10 cyclische belastingen gedaan. Begonnen werd met 250 Newton (N) waarna de belasting verhoogd werd naar 500 N, 1000 N, 1500 N etc. De test werd gestaakt wanneer de met EF behandelde fractuur faalde. Dit falen werd gedefinieerd als een afname van meer dan 5 graden in de NSA (gemeten tussen twee cycli) of een abrupte reductie van 50% in de toegepaste gemeten belasting. Tijdens de belasting werd de beweging in de fractuur gemeten. Aan het einde van het experiment werden de heupbotten opgelost in zoutzuur (H2SO4) om zo alleen het elastomeer over te houden. Hierna kon, door onderdompeling in water, het volume van ingespoten elastomeer gemeten worden.

De belasting waarbij de met EF behandelde fracturen faalde was gemiddeld 2709 Newton. Deze belasting is aanzienlijk hoger dan de normale belasting gemeten ter hoogte van de heup tijdens het lopen, i.e. gemiddeld 2 keer het lichaamsgewicht of te wel 1500 N bij 75kg. De gemiddelde beweging tussen de fractuurdelen was 3.16 mm. We vonden geen correlatie tussen de belastbaarheid en het volume elastomeer. Dit experiment toont aan dat een gebroken kadaverheup die preventief behandeld is met EF, belast kan worden met bijna twee keer zoveel kracht als nodig is bij het lopen. Toekomstig *in vivo* onderzoek moet de preventie van dislocatie na belasting van EF behandelde heupen bevestigen. In ***Hoofdstuk 8*** beschrijven we de mogelijkheden van osteosynthese als "back-up" in het geval van een gefaalde preventieve EF na fractuur. Bijvoorbeeld in het geval van dislocatie direct na de fractuur (primaire dislocatie) of dislocatie na belasting (secundaire dislocatie). Het moet dan alsnog mogelijk zijn om met standaard chirurgische technieken en implantaten deze heupfracturen te fixeren. Hiervoor zijn 10 gepaarde kadaverbotten gebruikt. Binnen elk paar werd gerandomiseerd voor EF behandeling of controle. De heupen werden gebroken in een gestandaardiseerde val-opstelling. Hierna werden de fracturen behandeld met twee typen implantaten (DHS of PFNA) afhankelijk van het type fractuur. De tijd die nodig was om het implantaat in te brengen werd geregistreerd en technische complicaties

werden beschreven. Na het inbrengen van het implantaat werden de heupen getest in de staande positie in de testbank. We vonden geen verschil in de operatietijden tussen EF en controlegroep en er was ook geen verschil in de belastbaarheid na het inbrengen van de implantaten. Er was geen speciaal instrumentarium nodig om het elastomeer te verwijderen, in tegenstelling tot bijvoorbeeld bij cement femoroplasty te verwachten is. Ook waren geen technische complicaties bij het inbrengen van de implantaten. Dit onderzoek bevestigt ons vermoeden dat er geen beletsel is voor het inbrengen van een implantaat in het geval van dislocatie na preventieve EF behandeling.

In ***Hoofdstuk 9*** wordt de trombogeniciteit van het voor EF gebruikte elastomeer beschreven. Het elastomeer dat gebruikt is in EF is identiek aan het elastomeer dat gebruikt wordt voor de applicatie "Customized Aortic Repair (CAR)". De trombogeniciteit als onderdeel van de biocompatibiliteit van het elastomeer is van belang voor de toepassing van CAR, aangezien het elastomeer bij deze toepassing direct in de bloedbaan wordt gebracht. Daarnaast zou trombogeniciteit en zeker hyper-trombogeniciteit van het elastomeer een rol kunnen spelen bij EF. In het geval van hyper-trombogeniciteit zou onverhoopte lekkage van elastomeer richting het veneuze systeem bijvoorbeeld kunnen leiden tot veneuze trombose. In dit onderzoek hebben we gekeken naar de expressie van de stollingsfactoren Fibrinopeptide A (FPA) en P-selectin in het bloed van gezonde vrijwilligers. We hebben een eerder gevalideerd ex-vivo model gebruikt waarbij het bloed werd geaspireerd uit een vene in de elleboogplooi, door een buisje gemaakt van elastomeer. De controle was de andere arm van de gezonde vrijwilliger en een buisje van ePTFE, dit is de gouden standaard kunststof in bypass chirurgie. Het bloed werd met vaste intervallen opgevangen aan het einde van het elastomeer of ePTFE buisje. In deze samples werden de FPA en P-selectin gemeten. Uit deze metingen blijkt dat het gebruikte elastomeer een lage trombogeniciteit heeft, vergelijkbaar met een standaard vaatprothese van ePTFE. Ideaal voor de toepassing CAR en ongevaarlijk in EF.

CONCLUSIE EN TOEKOMSTPERSPECTIEVEN

Demografische veranderingen gaan in de komende decennia leiden tot een toename van het aantal heupfracturen. Deze fracturen hebben een hoge mortaliteit (tot 30% in het eerste jaar), maar hebben vooral een enorm negatieve impact op de kwaliteit van leven van de patiënt en zijn omgeving. Ondanks de tot op heden ingestelde preventieve maatregelen, met name gefocust op de medicamenteuze behandeling van osteoporose, neemt de prevalentie van eerste en tweede heupfracturen niet af. Juist bij de behandeling van die tweede heupfracturen zijn de postoperatieve complicaties bijna verdubbeld en is er een toegenomen institutionalisering na ontslag uit het ziekenhuis. Het ligt dan ook voor de hand om ons eerst te richten op de preventie van tweede heupfractuur chirurgie. EF contralateraal ingebracht tijdens de ipsilaterale chirurgie geeft dan een direct preventief effect, het is niet duur en er is geen extra operatiezitting of extra anesthesie nodig. De toegenomen morbiditeit wordt zeer laag ingeschat. In biomechanische en biocompatibiliteits experimenten beschreven in dit proefschrift is de effectiviteit van EF als preventieve modaliteit in vitro aangetoond.

Toekomstig onderzoek naar de effectiviteit en veiligheid van EF in vivo lijkt een logische stap. Bij elke preventieve behandeling moeten de negatieve effecten van die behandeling voor degene die de behandeling nooit nodig hebben, in evenwicht zijn met de positieve effecten bij degene die de behandeling wel nodig blijken te hebben (10-16% tweede heupfracturen). Het preventief behandelen van alle contralaterale heupen met EF tijdens de eerste fractuur zou dus een aanzienlijke overbehandeling kunnen betekenen (84% - 90%). Echter door de minimale extra belasting en lage kosten van EF enerzijds, en een groot verlies aan kwaliteit van leven en hoge kosten bij een tweede heupfractuur anderzijds, zal contralaterale EF bij alle eerste heupfracturen zeker effectief blijken. Door nauwkeurige selectie van patiënten met het hoogste risico op een tweede heupfractuur, zal de effectiviteit van de preventieve behandeling met EF nog verder stijgen.

Dierexperimenteel onderzoek naar het effect van EF op de vascularisatie van het omliggende bot en mogelijke systemische en trombo-embolische bijwerkingen van intra-ossale toediening van het elastomeer kunnen belangrijke nieuwe stappen zijn. Daarnaast kunnen we door gebruik te maken van Roentgen Stereophotogrammetric Analysis (RSA) een indruk krijgen van de genezing van een fractuur in een preventief met EF behandelde heup. Met RSA kunnen in 3 dimensies verplaatsingen van de fractuurdelen tot 0.1mm en 0.1 graden gemeten worden. Bovengenoemde onderzoekingen zullen onderdeel zijn van een gefaseerde introductie van deze nieuwe medische technologie, met optimale patiëntveiligheid en kwaliteit van leven als belangrijkste doelen.

APPENDICES

CURRICULUM VITAE

The author of this thesis was born on June 11th 1972 in Schiedam, the Netherlands. He grew up in Leiden and later Oegstgeest, where he graduated from the Rijnlands Lyceum in 1991. After one year of medical school at the K.U. Leuven, Belgium, he continued his medical education at the Rijksuniversiteit Leiden in 1992. During the years in University, he worked as a car mechanic, restoring old-timers. Furthermore he worked as an allocation coordinator for the Eurotransplant International Foundation. In 1998, following in the footsteps of many renowned Dutch (vascular) surgeons and supervised by Prof. dr. O.T. Terpstra, he moved to California, United States of America and worked as a visiting researcher at the Dr. R.C. Robbins' Cardiothoracic Transplantation Laboratory at Stanford University.

In 2001 he attained his medical qualification, and started work as a surgical resident in Medisch Centrum Haaglanden in The Hague, the Netherlands. His surgical training started in 2002 under the supervision of Dr. J.C.A de Mol van Otterloo. In 2008 he completed his surgical training at the Leiden University Medical Center under the supervision of Prof. dr. J.F. Hamming. It was during this period that he initiated research and experiments leading to this thesis.

From 2008 to 2010 he received advanced surgical training in vascular and endovascular surgery (CHIVO) in the St. Elisabeth Hospital Tilburg under the supervision of Dr. D.P. van Berge Henegouwen and Dr. P.W.H.E. Vriens.

Since 2011 the author has been happily living in The Hague with Bregje and their children: Floor, Michiel, Iris and Sacha. He is a surgeon, specialised in vascular, endovascular and endocrine surgery at the Bronovo Hospital and Medisch Centrum Haaglanden.

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