Tibial shaft fracture

Incidence, short- and long-term outcomes

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PETER LARSEN

DISSERTATION SUBMITTED 2015

AALBORG UNIVERSITY
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Dissertation submitted

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ENGLISH SUMMARY

The incidence of tibial shaft fractures is reported to be between 17 and 21 per 100,000 persons representing 2% of all fractures and up to 40% of all long bone factures in adults. The treatment of tibial shaft fractures with intramedullary nailing has become the treatment of choice for adults. The operative procedure is described with high rates of union and low rates of complications. However, the outcome after a tibial shaft fracture treated with intramedullary nailing is commonly reported with knee and ankle pain, joint stiffness, development of degenerative joint disease, rotational malalignment, complications due to soft tissue injury, muscular weakness and limitations in activity of daily living and QOL.

The overall purpose of the present PhD thesis is to provide up-to-date information concerning epidemiology of tibial shaft fractures and to investigate the development in quality of life, pain and functional outcomes from surgery and onwards, following a tibial shaft fracture treated with intramedullary nailing.

Study I reported an incidence of 16.9/100,000/year from a complete and non-selected population. Study II reported the long-term patient-reported outcomes and showed that approximately 8 years after the fracture patients reported significantly worse outcome for 4 of the 5 KOOS subscales compared to the reference population. Study III suggested that localized, distal and bilateral hyperalgesia are common within the first 12 months postoperatively. Study IV reported that patients achieved a level of QOL close to an established reference population within the first 12 months postoperatively. However, study IV also showed a significant worse outcome in 3 of the 5 KOOS subscales compared to a reference population at 12-months follow-up. Moreover, this study showed that increasing difference in muscle strength for knee extension between legs was associated with a decreasing QOL.

The results of this thesis suggested that regaining pre injured QOL and muscle strength following a tibial shaft fracture takes considerable time. The current findings indicate that clinicians may take QOL, pain reactions, muscle strength and functional performance into account when planning rehabilitation programs to the patient group. Both generic and injury specific questionnaires may be required in evaluating outcomes following a tibial shaft fracture.

DANSK RESUME

Skaft fraktur på tibia er en almindelig forekommende fraktur og repræsenterer samlet set 2% af alle frakturer og op til 40% af alle frakturer i de lange rørknogler. Patienter med skaft fraktur på tibia tilbydes i reglen operation med marvsømning. Den operative procedure er rapporteret med få komplikationer, og er i dag standard til voksne patienter. Imidlertid er det ikke ualmindeligt at opleve patienter i klinikken, der efterfølgende klager over smerter fra knæ og ankel, ledstivhed, nedsat muskelkraft samt begrænsninger i aktivitet og nedsat livskvalitet.

Det overordnede formål med denne afhandling er at bidrage med up to date viden om epidemiologi fra en komplet dansk population med skaft fraktur på tibia. Desuden er formålet at undersøge udviklingen i livskvalitet, smerter og funktion, hos patienter behandlet med marvsømning efter en fraktur på tibia skaftet.

Studie I var et epidemiologisk studie med formålet at undersøge incidens og fraktur klassifikation hos en samlet population fra Region Nordjylland. Resultaterne viser en incidens på 16,9/100.000/år for skaft fraktur på tibia. AO type 42-A1 var den mest almindelige fraktur type (34%). Studie II var et retrospektivt tværsnitsstudie med det formål at se på de patient-rapporterede langtidseffekter (7.9 år) af fraktur på tibia. Resultaterne viser signifikant dårligere KOOS scores på 4 af 5 subgrupper i gruppen med fraktur sammenlignet med en referencepopulation. Studie III var et prospektivt follow-up studie med det formål at undersøge smerteudviklingen og hyperalgesi 6 uger, 3, 6 og 12 mdr. efter fraktur. Resultaterne viser en overordnet signifikant stigning i PPT for både det raske og opererede ben mellem alle måletidspunkterne på benene, men ikke på armene. Mellem det opererede og raske ben viser undersøgelsen en signifikant forskel efter 6 uger, 3 og 6 måneder men ikke efter 12 måneder. Studie IV var et prospektivt follow-up studie med det formål at undersøge korttidseffekterne på patient-rapporteret outcome, funktion og muskelstyrke. Resultaterne viser, at mænd ikke opnår en livskvalitet på niveau med en reference population, inden for de første 12 måneder. Ved 12 måneders opfølgning viser studiet signifikant dårligere KOOS scores i 3 af 5 subgrupper sammenlignet med en reference population. Desuden viser denne undersøgelse, at patienterne efter 12 måneder, har nedsat muskelstyrke i det opererede ben sammenlignet med det raske ben. En stigende forskel i muskelstyrke for knæ ekstension mellem benene var forbundet med en faldende livskvalitet.

Afhandlingens resultater fremhæver at det ofte tager lang tid at genvinde muskelstyrke, funktion og livskvalitet efter en skaft fraktur på tibia. En viden som klinikeren bør have med i sine overvejelser når det planlægges rehabiliteringsforløb for patientgruppen. Desuden peger resultaterne på, at både generiske og strukturspecifikke evalueringsredskaber bør benyttes ved effektvurdering af behandlingen.

PREFACE

The scientific work presented in this PhD thesis was performed at the Department of Occupational Therapy and Physiotherapy, Aalborg University Hospital and Aalborg University, Aalborg, Denmark. The work was conducted from September 2011 to September 2015 during my employment in the Department of Occupational Therapy and Physiotherapy, Aalborg University Hospital, Aalborg, Denmark.

The data collection for all the four studies included in this work was conducted at the Department of Occupational Therapy and Physiotherapy, Aalborg University Hospital, Aalborg, Denmark.

The PhD thesis is based on the following four manuscripts:

I: Incidence and epidemiology of tibial shaft fractures. /Larsen, Peter; Elsoe, Rasmus; Hansen, Sandra Hope; Graven-Nielsen, Thomas; Laessoe, Uffe; Rasmussen, Sten.
Published in: Injury, 2015; 46(4): 746-750.

II: Restrictions in Quality of Life after Intramedullary Nailing of Tibial Shaft Fracture. A retrospective follow-up study of 223 cases. / Larsen, Peter; Lund, Hans; Laessoe, Uffe; Graven-Nielsen, Thomas; Rasmussen, Sten.
Published in: Journal of Orthopaedic Trauma, 2014; 28(9): 507-512.

III: Local and widespread hyperalgesia after isolated tibial shaft fractures treated with intramedullary nailing. /Larsen, Peter; Elsoe, Rasmus; Graven-Nielsen, Thomas; Laessoe, Uffe; Rasmussen, Sten.
Accepted for publication in: Pain Medicine, September 2015 (in press)

IV: Decreased muscle strength is persistent and associated with worse Quality of Life one year after intramedullary nailing of a tibial shaft fracture. A prospectively observational study of 49 patients with 12 months follow-up. /Larsen, Peter; Elsoe, Rasmus; Laessoe, Uffe; Graven-Nielsen, Thomas; Eriksen, Christian Berre; Rasmussen, Sten.
Submitted in: Injury, August 2015

THESIS AT A GLANCE

The aim of the present PhD thesis was to report up-to-date information concerning epidemiology of tibial shaft fractures (study 1) and to investigate the development in quality of life, pain and functional outcomes from surgery and onwards, following a tibial shaft fracture treated with intramedullary nailing.
Short-term outcomes are presented in studies 3 and 4, and long-term outcomes in study 2.

Figure 1 outlines the relationship between the conducted studies on a time line. Table 1 shows the thesis at a glance.

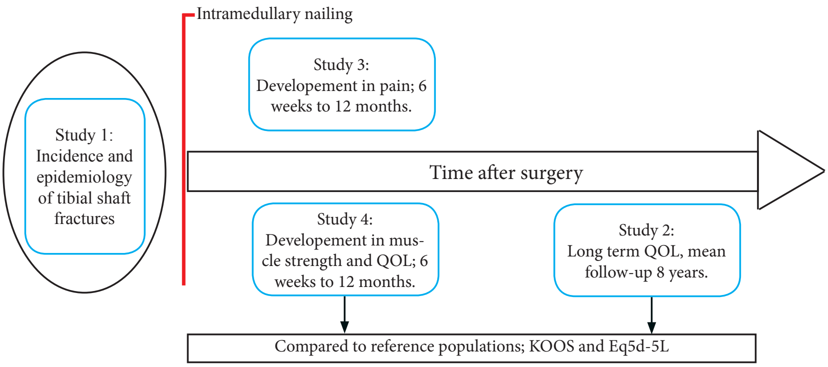

Figure 1: The relationship between the conducted studies and time after surgery of the study populations.

Study	Aim	Study design	Participants	Main outcome	Conclusion
1	Provide up-to-date information on the incidence of tibial shaft fractures in a large and complete population	Population-based retrospective study with reviews of clinical and radiological records.	196 patients were treated for 198 tibial shaft fractures in the years 2009 and 2010	Incidence XX/100,000/year	This study shows an incidence of 16.9/100,000/year for tibial shaft fractures. AO-type 42-A1 was the most common fracture type, representing 34% of all tibial shaft fractures.
2	Evaluate long term outcome of knee pain, limitations in activity and QOL using an injury specific questionnaire.	Retrospective, Cross sectional study	223 patients agreed to participate	KOOS score	At an average of 8 years after a tibial shaft fracture 60% of the patients experience limitations in Function in sport and recreation, 58% restrictions in QOL and 44% reported increased incidence of knee pain compared with a reference population. This was mainly evident among the young participants.
3	Assess the pain and hyperalgesia from 6 weeks to 12 months postoperatively after intramedullary nailing of an isolated tibial shaft fracture.	12 months prospectively follow-up study	39 patients were included	Pain pressure thresholds (PPT)	This study suggests that localized, distal and bilateral hyperalgesia are common following an isolated tibial shaft fracture treated with intramedullary nailing, although no widespread hyperalgesia was detected.
4	Evaluate patient-reported short-term outcomes in the period from surgery to 12 months postoperatively.	12 months prospectively follow-up study	49 patients were included	Eq5d-5L index	Within 12 months after surgery patients achieve a QOL level close to an established reference population. A statistically significant association between decreased muscle strength and worse QOL was observed.

Table 1: Thesis at a glance

ACKNOWLEDGEMENTS

This PhD thesis was accomplished with the help and support of several people to whom I would like to express my gratitude.

First, I am grateful to all patients for participating and spending time with me in the laboratory. I am grateful to the staff, colleagues and friends in the Department of Orthopaedic Surgery and the Department of Physiotherapy at Aalborg University Hospital for contributing to a great work and research relationship and many exciting discussions during my years as a PhD student.

I would like to thank all my supervisors, Sten Rasmussen, Uffe Læssøe and Thomas Graven-Nielsen, for agreeing to take part in this project and for introducing me to the exciting world of clinical science. All of your critical questions, on-going discussions and help have been invaluable, and without your support this project would have been impossible.

I am grateful to the head of the Department of Physiotherapy, Aalborg University Hospital Hans Erik Lind Madsen and the physiotherapists Jan Kjærsgaard and Jane Andreasen, all for providing unrestricted time to work with this PhD project. Thanks for your understanding, flexibility and never ending support.

I am sincerely grateful to my friend and research fellow Rasmus Elsøe. Thanks for always taking time for our countless discussions on studies, clinical research, orthopeadics and life. Thanks for making the PhD years funny and for being a good friend. Without you this thesis would have been impossible.

Finally, of course thanks to my family and friends for your love, patience and support throughout this work.

TABLE OF CONTENTS

ABBREVIATIONS

QOL – Quality of life

PPT – Pain pressure thresholds

ROM – Range of motion

KOOS – Knee Injury and Osteoarthritis Outcome Score

VAS – Visual analogue scale

MVC – Maximum voluntary contraction

SD – standard deviation

BMI – body mass index

CT – computer tomography

ANOVA – Analysis of variance

RM – Repeated measurement

95% CI – 95% confidence interval

N – number

CHAPTER 1. BACKGROUND

1.1. A BRIEF HISTORICAL PERSPECTIVE IN TREATMENT OF TIBIAL SHAFT FRACTURE

The development from the fist recorded examples of intramedullary nailing in the 16th. century in Mexico [1] to intramedullary nailing becoming the treatment of choise [2-5], for diaphyseal fractures, has been long and fascinating [2]. The cornerstone in the treatment of tibial shaft fractures was the introduction of metal nails following Word War I by Hey Groves of England [2]. The modern technique of intramedullary nailing, including reaming and V-shaped nails, was developed in Germany by Küntscher in the 1940s [2,6]. Several modifications to the intramedullary nails, the development of surgical procedures and the introduction of locking screws have all been important steps in intramedullary nailing becoming the treatment of choice for shaft fractures of the tibia.

1.2. TIBIAL SHAFT FRACTURE

The incidence of tibial shaft fractures is reported as between 16 to 21 per 100,000 persons representing 2% of all fractures and up to 40% of all long bone fractures in adults [7,8]. A decreasing incidence and change in fracture patterns from the 1970s and onwards are reported in a number of studies [8-11]. The majority of patients with tibial shaft fractures are young, and a bimodal distribution with increased incidence in younger males and older females is reported [8,9]. Weiss et al [8] reported a median admission age of 28 years for males and 51 years for females from a Swedish national epidemiological database, including 10,627 patients in 2004. The distribution of tibial shaft fractures according to the AO-classification [12] is reported as: AO 42A-: 54%, 42 B-: 27.8% and 42 C-: 18.3%. AO type 42 A3 was the most frequent fracture type followed by the A1 and the A2 group [10]. Closed fractures of the tibial shaft are most common, and reported with a frequency between 76.5% and 88.0% of all tibial shaft fractures [8,10]. The literature lacks recent population-based epidemiology of the incidence, trauma mechanism and fracture classification of tibial shaft fractures, and no Danish studies exist.

1.3. INTRAMEDULLARY NAILING

The treatment of tibial shaft fractures are reported with a number of different treatment methods, including closed reduction and cast, intramedullary nailing and treatment with screws, plates and external fixation [8].

The treatment of tibial shaft fractures with intramedullary nailing has become the treatment of choice in adults in recent decades [3,13]. The operative procedure with intramedullary nailing is described with a high rate of union and a low rate of complications [7]. Non-unions are reported between 1% and 6% in closed tibial shaft fractures [6,14-16] and between 12% and 49% in open fractures [6]. Court-Brown et al. [6] reported the time to union for 859 closed tibial diaphyseal fractures as a mean of 18.5 weeks and a mean time to union of 30 weeks in 247 open diaphyseal tibial fractures. The incidence of infection following treatment of tibial shaft fractures with intramedullary nailing is reported between 0% and 3% in closed tibial shaft fractures [6]. In open fractures the incidence of infection is reported between 7% and 23% [6]. Moreover, complications such as mal-unions, compartment syndrome, soft tissue infection and necrosis, migration of the nail and broken locking screws are described in the literature with varying, but uncommon, incidences [6].

1.4. PATIENT-REPORTED AND OBJECTIVE OUTCOMES FOLLOWING TIBIAL SHAFT FRACTURES

Knee pain is a common complication to intramedullary nailing of tibial shaft fractures [6,17,18]. The incidence of knee pain is reported between 10% and 80% in a number of studies with varying follow-up times [3,14,17,19,20]. Keating et al. [18] reported, knee pain in 57% of patients after intramedullary nailing of the tibia, with a mean follow-up period of 32 months postoperatively. Although pain is well known as a common complication, no studies have systematically studied the pain sequel and no studies have reported on hyperalgesia or spreading sensitisation in patients following a tibial shaft fracture, treated with intramedullary nailing. Several reasons for anterior knee pain have been suggested [17,18,21-23], but the ethiology is not fully established.

Patient-reported QOL and function have been reported in several papers with varying outcomes by authors such as Court-Brown, Skoog, Toivanen, Habernek, Keating, Lefaivre and Vaisto [6,17-20,24-26]. Lefaivre et al. [3] reported a comparable level of function compared to an established population norm, according to the SF-36 questionnaire with 14 years of follow-up. A recent cross sectional study by Connelly et al. [27] reporting the outcome of 1502 tibial shaft fractures 12 to 22 years postoperatively and reported a good overall long-term functional outcome measured with the SF-12 questionnaire.

However, clinical practice frequently demonstrates patients with limitations in function and restrictions in QOL after intramedullary nailing of tibial shaft fractures. Skoog et al. [24] supported this clinical experience and reported that patients following a tibial shaft fracture had not recovered fully to the pre-injury QOL neither 4- nor 12-months postoperatively, according to the SF-36 questionnaire.

Most studies evaluating patient-reported outcomes after tibial shaft fractures are conducted using generic QOL questionnaires such as SF-36, SF-12 and Eq5d-5L, and the literature lacks studies reporting injury/structure-specific patient-reported outcomes that are, specific for knee related disabilities. Generic questionnaires may lack responsiveness for injury-specific changes – a responsiveness that might be found in an injury/structure specific questionnaire.

A number of studies have reported an association between knee pain and worse patient-reported function following tibial shaft fractures [17,27]. Keating et al. [18] reported that knee pain was activity related in 92% of patients. Of the 57% reporting knee pain, 44% had restrictions in leisure activities and 22% were unable to return to their pre-injury activities [18]. These findings are supported by Boyd et al. [28] who reported that pain interfered with activity of daily living in 37% of patients, and that 57% experienced limitations in sports activity, following a tibial shaft fracture.

Several studies have reported decreased muscle strength following a tibial fracture [19,20,29,30] but no studies have described the association between the development in muscle strength postoperatively and the patient-reported QOL. In a prospective study, Gaston et al. [30] reported that two weeks after a tibial fracture, the knee flexor and extensor muscles are reduced to about 40% of normal power, which increases to between 75% and 85% after one year. Gaston et al. [30] did not compare the decreased muscle force to patient-reported function, difference in muscle function between legs or patient-reported QOL. Moreover, Väistö et al. [19,26] reported, a decreased muscle force for knee extension and flexion in the injured leg with a long-term (3.2 and 8.1 years) follow-up. This was especially pronounced for knee extension and for patients with knee pain.

However, the literature is contradictory regarding outcomes after tibial shaft fractures treated with intramedullary nailing. It is commonly reported that knee and ankle pain, joint stiffness, development of degenerative joint disease, rotational malalignment, complications due to soft tissue injury, muscular weakness and limitations in activity of daily living and QOL are complications with the treatment of tibial shaft fractures [3,6,17-20,22,23,31-37]. Even though a large number of studies are available on this topic, the understanding of the development in patient-reported function, QOL, muscle strength and pain following a tibial shaft fracture, are still not fully established.

CHAPTER 2. GENERAL AIM OF THE THESIS

The aim of the present PhD thesis was to provide up-to-date information concerning epidemiology of tibial shaft fractures and to investigate the short- and long-term development in quality of life, pain and functional outcomes following tibial shaft fractures treated with intramedullary nailing.

2.1. SPECIFIC AIMS

Study I: To provide up-to-date information on the incidence and epidemiology of tibial shaft fractures in a complete regional Danish population.

Study II: To evaluate the long-term outcome in patient-reported QOL, knee pain, and limitations in activity following intramedullary nailing of a tibial shaft fracture.

Study III: To assess the development in pain and hyperalgesia from 6 weeks to 12 months postoperatively after intramedullary nailing of an isolated tibial shaft fracture.

Study IV: To evaluate the development in patient-reported QOL, muscle strength and function in the period from 6 weeks to 12 months postoperatively after intramedullary nailing of an isolated tibial shaft fracture.

2.2. HYPOTHESIS

Study I: No specific hypothesis was highlighted a priori to this study. The literature lacks recent population-based epidemiology studies of the incidence, trauma mechanism and fracture classification of tibial shaft fractures and no Danish studies exist.

Study II: It was hypothesised that knee pain, limitation in activity and participation, and restrictions in knee related quality of life are significant long-term components after treatment of tibial shaft fractures with locked intramedullary nailing. Furthermore, it was hypothesised that long-term outcome varies with age and gender.

Study III: It was hypothesised that patients treated after a tibial shaft fracture with intramedullary nailing would experience hyperalgesia in the injured leg from the time of fracture to 12 months postoperatively. Furthermore, it was hypothesised that a group of patients would present with bilateral hyperalgesia and spreading sensitisation.

Study IV: The hypothesis was that patients treated for a tibial shaft fracture with intramedullary nailing would experience an increase in QOL and muscle strength throughout a 12 months follow-up period. At 12 months postoperatively patients would report worse QOL and functional outcome compared to an established reference populations. Patients would demonstrate decreased muscle function in the injured leg compared to the non-injured leg from the time of injury to 12 months postoperatively. Decreased muscle strength is associated with worse QOL and functional outcome.

CHAPTER 3. METHODS AND MATERIALS

3.1. DESIGN

Four studies were included in the present PhD thesis. The first study was of a retrospective population-based epidemiological design (I). The second study was of a retrospective cross-sectional design (II), and two studies were designed as observational prospective follow-up studies (III and IV).

3.2. STUDY POPULATIONS

Study I

All patients treated for a tibial shaft fracture (AO classification 42 - [12]), in the North Denmark region, Denmark, in the years 2009 and 2010 were included. The study was based on an average population of 580,072. The region is served by Aalborg University Hospital (level 1 trauma centre) and six minor hospitals, all included in this study population.

A total of 196 patients were treated for 198 tibial shaft fractures during the study period.

This study was conducted in accordance with the ethical standards of the responsible committee and with the ethical principles of the 1975 Declaration of Helsinki. The study was approved by the Danish Data Protection Agency (J. nr. 2010-41-4354).

Study II

All patients treated by reamed and locked intramedullary nailing following a tibial shaft fracture at Aalborg University Hospital, Denmark were identified in a period from 1998 to 2007, both years included. The patients were identified by searching the medical chart system. All fractures of the tibial shaft (diaphyseal fracture) were included, AO classification 42- [12]. Metaphyseal fractures were excluded. Only patients alive at the time of follow-up were included. Patients less than 18 years of age at the time of follow-up were excluded. Patients who were unable to participate due to mental disabilities were excluded.

A total of 294 patients were enrolled in the study.

The study was approved by the Danish Data Protection Agency (J. nr. 2010-41-4354). The study was presented to the local ethics committee and was deemed as not notifiable due to the design and lack of intervention. The head of the Orthopaedic Trauma Unit approved the study.

Study III

All patients treated with intramedullary nailing after a tibial shaft fracture (AO classification 42-[12]), with or without a fracture of the fibula bone between September 2012 and April 2014 at Aalborg University Hospital, Denmark, were included in this prospectively 12 months follow-up study. Patients with tibial shaft fractures who were treated without intramedullary nailing, patients with pathological fractures and patients with bilateral fractures were excluded. Patients with metaphyseal fractures were excluded. Patients who were unable to participate due to mental disabilities were excluded.

All participants gave written informed consent at the time of admission to the hospital.

A total of 39 patients were treated for a tibial shaft facture with intramedullary nailing during the study period.

The study was approved by the Danish Data Protection Agency (J. nr. 2008-58-0028) and the local ethics committee (J.nr: N-201-200-11), and performed according to the principles of the Helsinki declaration. Oral and written information was provided to the patients, and a written consent form was obtained from all patients.

Study IV

All patients treated with intramedullary nailing after a tibial shaft fracture (AO classification 42 - [12]), with or without a fracture of the fibula, between September 2012 and June 2014 at Aalborg University Hospital, Denmark, were included in in this prospectively 12 months follow-up study. Patients with tibial shaft fractures who were treated without intramedullary nailing, patients with pathological fractures and patients with bilateral fractures were excluded. Patients with metaphyseal fractures were excluded. Patients who were unable to participate due to mental disabilities were excluded.

A total of 49 patients were treated for a tibial shaft fracture with intramedullary nailing during the study period.

The Danish Data Protection Agency (J. nr. 2008-58-0028) and the local ethics committee (J.nr: N-201-200-11) approved the study, and it was performed according to the principles of the Helsinki declaration. Oral and written information was provided to the patients, and a written consent form was obtained from all patients.

3.3. OUTCOME MEASUREMENTS USED IN THIS PHD THESIS

Patient-reported measurements

Eq5d-5L is a standardised and validated instrument to assess health outcomes [38]. It consists of five dimensions: mobility, self-care, usual activities, pain/discomfort, anxiety/depression and a self-rated health scale on a 20 cm vertical, visual analogue scale with endpoints labelled 'the best health you can imagine' and 'the worst health you can imagine'. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems and extreme problems. A Danish data set was used to calculate the Eq5d-5L index [39]. An Eq5d-5L index at 1.0 indicated full health, and 0.0 denoted death. A reference population from Denmark is available [40].

The Knee Injury and Osteoarthritis Outcome Score (KOOS) [41] is a standardised and validated instrument used in order to evaluate knees and associated problems. The questionnaire includes 42 items, and each item obtains a score between 0 and 4; a total score of 0 to 100 was calculated for each subscale. A total score of 100 indicated no symptoms, and 0 indicated major symptoms. KOOS reference data [42] from a general population-based sample in southern Sweden is available.

Objective assessments

Range of motion (ROM). The patients range of motion of the knee at the injured leg was assessed by active extension and flexion with the patients supine on the examination table. The patients were asked to perform maximal flexion and extension, and the angle was measured by a goniometer. The intra-tester reliability of the goniometer measurement of knee motion is generally reported with high ICC values (ICC 0.78-0.99) [43]. Ankle range of motion of the injured leg was assessed by active dorsal and plantar flexion of the talocrural joint with the patients supine on the examination table. The patients were asked to perform maximal dorsal and plantar flexion, and the angle was measured with a goniometer. The intra-tester reliability of the goniometer measurement of ankle motion is generally reported with moderate to high ICC values planter flexion (ICC 0.47-0.99) and dorsal flexion (ICC 0.64-0.97) [43].

Isometric muscle strength was measured by a strap-mounted dynamometer attached to the wall (Mecmesin AFG2500, Mecmesin Ltd, West Sussex, UK). The strap-mounted isometric test was performed for knee flexion and knee extension for both legs. While the patients sat on an examination table in an upright position, the strap was placed around their foot and attached to the dynamometer fixed to a wall. The patients were asked to perform a maximal voluntary contraction (MVC) for 3 to 4 seconds. A pause of 30 seconds was maintained between the tests. All measurements were repeated twice, and the highest value was used for analysis. The test set-up was described and validated by Rathleff et al. [44]. The intra-tester reliability of the test is reported with high ICC values >0.92 [44].

Functional performance was assessed by the 30-seconds chair-to-stand test. The patients were asked to stand and sit as many times as possible in a period of 30 seconds from a standard height (43 cm) chair without armrests. The number of times they stood was the outcome measure [45]. The intra-tester reliability of the test is reported with high ICC values >0.97 [46].

Pain measurements

The pain intensity of the injured leg for the worse pain during the last 24 hours and rest pain was measured on a 10 cm visual analogue scale (VAS) with the endpoints "no pain" and "maximal pain."

The pressure pain sensitivity was assessed by pressure pain thresholds (PPTs) recorded by a handheld pressure algometry (Algometer Type II, Somedic AB, Sweden). Pressure was applied at a rate of 30 kPa/s with a 1 cm^2 probe until the patient perceived the pressure as painful and pressed the stop button. If the test exceeded 1000 kPa, it was interrupted and 1000 kPa was documented as the test result. The PPT was assessed bilaterally at six sites in the knee region and one site on the forearm (Figure 3-1). All PPT assessment sites were assessed twice and each recording was separated by approximately 5 seconds. The average of two PPT measurements from all seven sites, respectively, was calculated and used for further analysis. The intra-tester reliability of the test is reported with high ICC values >0.84 [47].

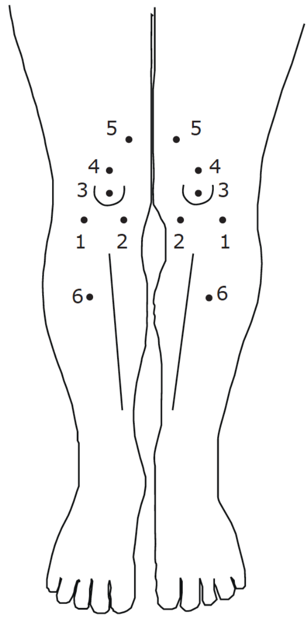

Figure 3-1: Locations of pressure pain threshold points on the lower extremity.1. 2 cm distally to the inferior lateral edge of the patella. 2. 2 cm distally to the inferior medial edge of the patella. 3. Centre of the patella. 4. 2 cm proximally to the superior edge and the patella. 5. M. vastus medialis. 6. M. tibialis anterior. (5 cm. distally of the tibial tuberosity). 7. M. extensor carpi radialis longus (5 cm. distally to the lateral epicondyle of the humerus; not illustrated)

Radiological outcome measurements

Radiological examinations were performed preoperatively and at 6 weeks, 3 months, 6 months and 12 months postoperatively. Fracture classification was carried out according to the Orthopaedic Trauma Association Classification (AO) [12] and was conducted on the preoperative X-rays. The AO fracture classification groups the fractures from simple to complex and indicates the site of the fracture.

Evaluation of fracture union and alignment was based on postoperative X-rays of the fractured lower leg and clinical examination of the fracture site. Radiological examinations were performed at 6 weeks, and at 3, 6 and 12 months postoperatively. The radiological assessments were made on AP and side X-rays. The evaluation of union were defined as: *i*) visible callus formation on at least three of four sides, no visible fracture line and no pain from fracture at weight-bearing and following clinical examination (defined as: union), *ii*) visible callus formation on at least one of four sides, with a visible fracture line (defined as: partial union), and *iii*) visible fracture lines and no visible callus formation (defined as: no union). The evaluation of union was performed in agreement with other studies of evaluation union after fractures [48,49]. Two authors carried out radiological evaluations separately. In case of disagreement, consensus was obtained.

3.4. PROCEDURES

Study I
The primary outcome measurement was the incidence of tibial shaft fractures. Retrospective reviews of clinical and radiological records of the 196 patients included were conducted in June 2014.

Clinical information concerning age, gender, trauma mechanism and high- or low-energy trauma was obtained. High-energy trauma was defined as a fall from >3 metres or fracture due to a traffic accident at more than 30 km/h. The trauma mechanism was divided into car, motor cycle, other motorised vehicle, bi-cycle, sports, fall from a height of more than 3 metres, walking outdoors, and indoor activities such as falls and slips. Information about length of hospital stay, time to theatre following admission, conservative or operative treatment and multi-trauma was recorded.

All fractures were classified according to the AO classification [12]. Classification of the fractures was performed using preoperative X-rays or computer tomography (CT) when available.

Study II
The primary outcome was the KOOS questionnaire. All patients were contacted by mail, informed of the study, and asked to fill out the KOOS questionnaire in April 2010. If the patient did not reply, a second request was sent by mail. Finally, if there was still no reply, patients were contacted by telephone.

With a review of the patients' charts, fractures were classified as open or closed fracture. Removal of the nail, locking screws and additional damage such as other fractures were recorded. Complications such as compartment syndrome, deep infection, re-operation due to of non- or mal-unions were recorded. Retrospective chart reviews and KOOS collection were performed by one person (PL).

Study III
The primary outcome measurement was the pain pressure threshold (PPT). Patients' baseline characteristics were obtained at the time of admission to hospital. Information about age, gender, body mass index (BMI), trauma mechanism, type of trauma, fracture classification, type of surgery and complications were registered.

All patients were systematically examined according to pain pressure thresholds and pain intensity at the outpatient clinic at 6 weeks, 3 months, 6 months and 12 months postoperatively. The data collection was performed by one person (PL).

Study IV

The primary outcome measurement was the Eq5d-5L index [38]. The patients' baseline characteristics were obtained at the time of admission to the hospital. Information about age, gender, body mass index (BMI), trauma mechanism, type of trauma, fracture classification, type of surgery and complications were registered.

All patients were systematically examined at the outpatient clinic at 6 weeks, and at 3, 6 and 12 months postoperatively. Information concerning patient-reported outcome (Eq5d-5L and KOOS), objective assessments (isometric muscle strength, knee range of motion, 30-seconds sit-to-stand test and pain intensity) were measured at all follow-ups in the outpatient clinic. Test of maximal isometric muscle strength of the fractures leg was performed at 6- and 12-months follow-up. The data collection was performed by one person (PL).

3.5. STATISTICS

Study I

The assumption of normal distribution of the variables was checked visually by QQ-plots. Mean values and standard deviations are given for continuous variables. Frequencies and percentages are used for categorical data.

Incidences were calculated as the proportion of cases per 100,000/persons/year over the two-year (2009-2010) observational period, and were based on an average population of 580,072 citizens in the North Denmark region, Denmark during the study period.

Study II

Sample Size was limited to the number of patients with available medical records in the computer system at the hospital.

The assumption of normal distribution variables was checked visually by QQ-plots. KOOS-data in this study was for some parameters not normally distributed, but the sample size was large enough to apply the central limit theorem. Continuous data were expressed with mean and standard deviations. Categorical data were expressed as frequencies. Gender groups and four age groups were defined (18-34, 35-54, 55-74, and 75+ years) to study age and gender-related difference. The age group between 75-99 (n=11) was too small to be incorporated in the statistical analysis. Analysis of variance (ANOVA) and post hoc test was used to compare KOOS subscales and age related difference. An independent sample t-test was used to compare charts information and KOOS-data. A P-value < 0.05 was considered statistically significant.

Study III

The sample size was calculated based on a hypothesis that 12 moths postoperatively, patients following a tibial shaft fracture showed a difference in PPT levels (data from sites 1–6 combined) between the injured and non-injured leg. A difference of at least 20% in the PPT levels was considered the threshold. Because no previous studies have been conducted on this topic, an initial standard deviation was calculation based on the first 10 patients included in the study. With a standard deviation of 130 and a calculated mean difference between the legs of 20% (power of 80% and a significance level of 0.05), 31 patients were needed. To account for the observed relatively large variation and the risk of dropouts in the 12- month observation period, 40 patients were included.

The assumption of normal distribution of the variables was checked visually by QQ-plots. Continuous data were expressed as mean and standard deviation. Categorical data were expressed as frequencies.

A two-way mixed-model repeated measures analysis of variance (RM-MX-ANOVA) was used for the analysis of the differences in PPTs between the factors *time* (6 weeks, 3, 6 and 12 months postoperatively) and *leg* (non-injured and injured leg). If significant factors or interactions were found, multiple post hoc analyses with Bonferroni corrections were used. A two-way mixed-model repeated measures analysis of variance (RM-MX-ANOVA) was used to test the between-group difference in PPTs at the injured leg related to gender difference and whether the fracture was united or not. Spearman's rank test was used for analysis of the correlation between VAS pain and PPTs. A P-value of < 0.05 was considered significant.

Study IV

The sample size was calculated based on a hypothesis that 12 months postoperatively, patients following a tibial shaft fracture reported clinical worse Eq5d-5L compared to an established reference population [42]. The calculation was based on a reported minimal clinically relevant difference of 0.074 Eq5d-5L index point [50]. The standard deviation used to calculate the sample size was based on a previous study by Larsen et al. [51] on femoral shaft fractures, treated with intramedullary nailing, reporting a standard deviation of 0.172. The calculation was based on a power of 80% and a significance level of 0.05. This indicated that 43 patients were needed to show a clinically relevant difference. Due to uncertainty of variation and the risk of dropouts in the 12 months observation period 50 patients were included.

The assumption of normal distribution of the variables was checked visually by QQ-plots. Continuous data were expressed with mean and standard deviations. The Eq5d-5L was expressed with mean and 95% confidence intervals (95% CI). Categorical data were expressed as frequencies.

A two-way mixed repeated measures analysis of variance (RM-MX-ANOVA) was used to analyse the Eq5d-5L index, KOOS, ROM, pain, MVC, chair-to-stand test, pain and gender between the time points 6 weeks, and 3, 6 and 12 months postoperatively. If significant ANOVA factors or interactions were found, multiple pairwise analyses with post hoc-test (Bonferroni) corrections were used.
Spearman's rank test was used for analysis of the correlation between VAS pain, functional performance and difference in muscle strength between the injured and non-injured leg.

Either a linear or a logistic regression was used to conduct a uni-variate analysis, and generalised linear models were used for multivariate analyses of the variables affecting the patient-reported outcomes (Eq5d-5L index). The number of variables included in the multivariate analysis was limited to a P-value of <0.05. A P-value of < 0.05 was considered significant.

Statistical analysis was performed using SPSS (version 22) or STATA (version 13).

CHAPTER 4. SUMMARY OF RESULTS

4.1. STUDY I: INCIDENCE AND EPIDEMIOLOGY OF TIBIAL SHAFT FRACTURES

A total of 196 patients were treated for 198 tibial shaft fractures in the years 2009 and 2010. The mean age at time of fracture was 38.5 (21.2SD) years. The mean age for males was 32.8 (19.1SD) years, and for females 48.6 (21.1SD) years. The gender distribution was 71 (36.2%) females and 125 (63.8%) males.

The incidence of tibial shaft fracture was 16.9/100,000/year. For males, the incidence was 21.5/100,000/year, and for females, 12.3/100,000/year. Males have the highest incidence of fracture in the age group between 10 and 20 years: 43.5/100,000/year. Females have the highest incidence in the age group between 30 and 40 years: 21.3/100,000/year. In general, males present a higher incidence in the younger age groups below the age of 50. After the age of 50, females present a marginally higher incidence than males (Figure 4-1).

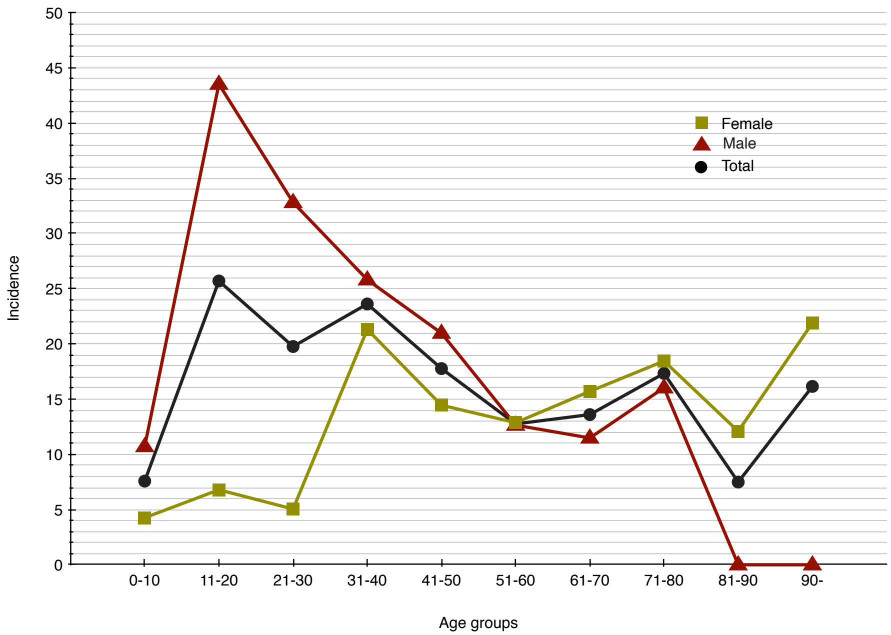

Figure 4-1: Incidence of tibial shaft fractures presented as number/100,000 persons/year.

AO-type 42-A1 was the most common fracture type, representing 34% of all tibial shaft fractures, followed by AO-type 42-A2 and B2 fractures, representing 15% of all fractures each. The distribution according to AO classification and trauma mechanism shows that the majority of tibial shaft fractures occur during walking, indoor activity and sports. The distribution among genders shows that males present a higher frequency of fractures while participating in sports activities and walking. Women present the highest frequency of fractures while walking and during indoor activities (Table 4-1).

AO 42-	High energy	Low energy	Multi trauma	Car	MC	OM	BC	Walking	Indoor	Sport	Fall from hights
A1	1	65	0	0	0	3	3	26	17	15	0
A2	14	19	8	4	1	4	0	13	3	8	0
A3	6	21	3	2	0	4	2	2	1	12	4
B1	4	26	2	0	2	3	1	6	10	8	1
B2	8	8	4	1	3	2	0	7	0	1	0
B3	2	3	1	1	0	1	0	1	0	2	0
C1	1	4	0	1	0	0	1	0	0	3	0
C2	4	2	2	0	2	1	0	1	1	1	0
C3	2	5	2	2	0	0	0	1	2	0	2
Total	**42**	**153**	**22**	**11**	**8**	**18**	**7**	**57**	**34**	**50**	**7**
Total women	7(17%)	64(42%)	3(14%)	2(18%)	1(13%)	2(11%)	1(14%)	31(54%)	22(65%)	9(18%)	2(29%)
Total men	35(83%)	89(58%)	19(86%)	9(82%)	7(88%)	16(89%)	6(86%)	26(46%)	12(35%)	41(82%)	5(71%)

MC (Motorcycle), OM (Other motorized vehicle), BC (Bicycle)
AO classification, missing N=1, due to missing information
Type of injury, missing N=3, due to missing information in medical charts

Table 4-1: The distribution according to AO classification and trauma mechanism.

4.2. STUDY II: RESTRICTIONS IN QUALITY OF LIFE AFTER INTRAMEDULLARY NAILING OF TIBIAL SHAFT FRACTURE. A RETROSPECTIVE FOLLOW-UP STUDY OF 223 CASES.

The demographics and clinical characteristics of the 223 patients included in the study group are shown in Table 4-2. The mean follow-up time was 7.9 years with a range from 3 to 13 years.

Characteristics of the 223 patients	
Patients, N (%) male/female	140(62.8%) / 83(37.2%)
Age follow-up, years (mean ± SD)	49.5±16.3
Age surgery, years (mean ± SD)	41.5±16.4
Fracture N (%) open/close	29(13%) / 194(87%)
Fracture fibula N (%) yes/no	165(74%) / 58(26%)
Unilateral fracture tibia N (%)	223(100%)
Additional damage*	29 (13,0%)
Removal of nail follow-up N (%)	32 (14.3%)
Complications N (%)	
Compartment syndrome	11 (4.9%)
Reoperation non- or malunions	8 (3.6%)
Reoperation deep infection	5 (2.2%)

*Table 4-2: Characteristics of the 223 patients included in the study population. N=number, SD=standard deviations, * =femur fracture, collum femoris fracture, malleol fracture and knee ligament injury*

KOOS data compared with reference data

Patients in the current study reported generally worse KOOS scores compared to the established reference population [42] for all the five KOOS subscales (Table 4-3). Of the five KOOS subscales four were significantly worse compared to the reference population, due to non-overlapping 95% CI. Compared to the mean of the reference group [42] 44% of the patients in the study group reported worse in the subscale Pain, 39% worse in the subscale ADL, 43% worse in the subscale Symptoms, 58% worse in QOL and 60% worse in the subscale Sport.

A comparison of the age related difference between the study group and the reference group showed that both genders in the age group 18-34 years reported significant difficulties in the subscales Pain, ADL, QOL and Sport, due to non-overlapping 95% CI. No significant differences were observed in the older age groups.

KOOS scores for study population and reference data

		KOOS PAIN	KOOS ADL	KOOS Symptoms	KOOS QOL	KOOS Sport
Total	N	223	223	223	223	221
	Mean	82.9	83.3	84.1	66.3	59.1
	SD	20.5	20.9	17.3	28.4	32.7
	95% CI	80.3-85.7*	80.4-86.0*	81.7-86.3	62.6-70.1*	54.7-63.4*
	Reference: 95% CI**	86,7-88.2	86.5-88.1	85.4-86.9	77.4-79.6	72.5-75.1

Table 4-3: KOOS score given as mean, standard deviation and 95%CI of the mean. The 95% CI of the mean for the reference group [42] is included.
** significant different from reference population, due to non-overlapping 95% CI.*
*** Unpublished data. Ewa Roos personal communication Nov 13, 2012. Paradowski et al. 2006 [42].*

Age related KOOS difference

The ANOVA test including KOOS subscales and the age groups (18-34, 35-54, 55-74 years) showed significant differences between age groups for Pain (ANOVA: $F_{2,211}$ =4.1, P=0.019), ADL (ANOVA: $F_{2,211}$ =3.5, P=0.032), QOL (ANOVA: $F_{2,211}$ =3.5, P=0.032) and Sport (ANOVA: $F_{2,211}$ =2.9, P=0.047).

The post-hoc tests showed that the age group between 18-34 and 35-54 years reported worse KOOS-scores compared to older age groups but is was only significant in the subscale Pain (Mean diff: 10.0, P=0.026).

4.3. STUDY III: LOCAL AND WIDESPREAD HYPERALGESIA AFTER ISOLATED TIBIAL SHAFT FRACTURES TREATED WITH INTRAMEDULLARY NAILING.

Demographics and clinical characteristics of the study group are shown in Table 4-4. Of the 39 patients included in the study, 35 completed the 12 months follow-up.

Baseline characteristics of the 39 patients	
Patients, male/female, N	24/15
Age at time of fracture, years, mean (range)	42.9 (18-79)
Height, mean (SD)	175.9 (11.8)
Weight, mean (SD)	77.6 (14.6)
BMI, mean (SD)	25.1 (3.7)
Smoker, yes/no	15/24
High/low-energy trauma, N	10/29
Fracture classification AO 42-, N	
A	25
B	10
C	4
Open/closed fracture, N	5/34
Fibula fracture, yes/no	36/3
Additional treatment besides intramedullary nailing	
Initial screw fixation of posterior aspect of the distal tibia, N	9
Metatarsal fracture treated with Kirschner-wires, N	1
Complications, N	
Compartment syndrome	1
Broken screws	1

Table 4-4: Characteristics of the 39 patients included in the study population. N=number, SD=standard deviations.

Postoperative development of pressure pain sensitivity

The development of outcomes for PPT measurements from 6 weeks after surgery to 12 months postoperatively for the injured and the non-injured leg is presented in Figure 4-2.

The mixed-model RM-ANOVA comparing all PPT sites at all time points and injured and non-inured leg showed a substantial main effect for time at all PPT sites except for the forearm (RM-MX-ANOVA: $F_{3,108} > 3.9$, $P < 0.012$), showing an overall progressive increase in PPTs between the 6-week and the 12-month time points. The post hoc pairwise multiple comparisons of the four time points postoperatively showed a significant increase in PPTs between 6 weeks and 12 months for PPT sites 1, 3 and 5 (P > 0.032). PPT site 1 and 5 showed a significant increase in PPTs between 3 months and 12 months (P > 0.012). Between the time point 6 weeks and 6 months PPT site 1 and 5 showed a significant increase (P > 0.03).

The analysis showed a significant effect between the injured and non-injured leg at all PPT sites except from site 7 at the forearm (RM-MX-ANOVA: $F_{1,34}$> 4.7, P < 0.040). The post hoc test showed significantly reduced PPTs (sites 1–6) in the injured leg compared to non-injured leg at all time points except from the time point 12 months (P > 0.04). At the time point 12 months postoperatively, no significant differences between the injured and non-injured leg were seen for PPT sites 1–7 (P > 0.062).

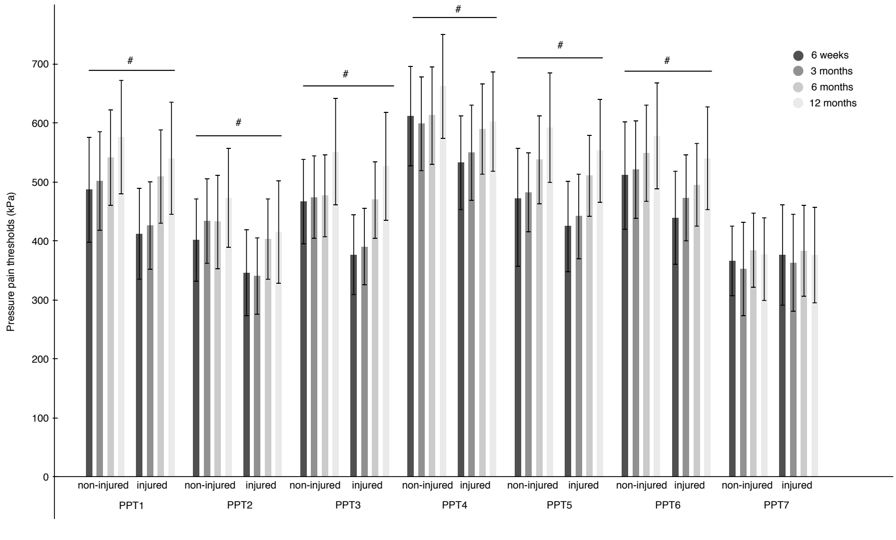

Figure 4-2: The temporal development of PPTs (mean, 95%CI) at sites 1 to 7, bilaterally, 6 weeks after surgery to 12 months postoperatively for the injured and the non-injured leg. The two-way RM-MX-ANOVA shows progressively increasing PPT levels at all sites (1-6) and reduced PPTs at the injured side compared with the non-injured side (1-6) except for the forearm from 6 weeks to 12 months postoperatively (#,P<0.012).

Correlations between pressure pain thresholds and pain intensity

At the time points 6 weeks, 3, 6 and 12 months after surgery, no statistically significant correlations between individual VAS scores (the worst pain during the last 24 hours) and mean PPT level (averaged data from sites 1–6 of the injured leg) were found (Spearman's rank test: *R* > 0.141, P < 0.404). The relationship between individual VAS scores (the worst pain during the last 24 hours) and PPTs on the forearm (site 7) at the four time points postoperatively showed no statistically significant correlations (Spearman's rank test: $R > -0.102$, $P < 0.564$).

4.4. STUDY IV: DECREASED MUSCLE STRENGTH IS PERSISTENT AND ASSOCIATED WITH WORSE QUALITY OF LIFE ONE YEAR AFTER INTRAMEDULLARY NAILING OF A TIBIAL SHAFT FRACTURE.

Forty-nine patients were included in the study population. Demographics and clinical characteristics of the study group are shown in Table 4-5. Of the 49 patients included in the study, 44 patients completed the 12 months follow-up.

Baseline characteristics of the 49 patients	
Patients, N male/female	32/17
Age at time of fracture, years, mean (range)	43.1(18-79)
Height, mean (SD)	176.0 (11.2)
Weight, mean (SD)	77.7 (14.6)
BMI, mean (SD)	25.1 (3.7)
Smoker, yes/no	18/31
High/low-energy trauma, N	12/37
Fracture classification AO 42-, N	
A	30
B	14
C	5
Open/closed fracture, N	6/43
Fibula fracture, yes/no	44/5
Additional treatment besides intramedullary nailing	
Initial screw fixation of posterior aspect of the distal tibia, N	14
Metatarsal fracture treated with Kirschner-wires, N	2
Complications, N	
Compartment syndrome	1
Broken screws	2

Table 4-5: Characteristics of the 49 patients included in the study population. N=number, SD=standard deviation

Patient-reported outcome

Twelve months postoperatively, the mean Eq5d-5L index was 0.829 (95% CI: 0.782–0.876). The mean Eq5d-5L VAS was 86.1 (95%CI: 80.8–91.4). The mean Eq5d-5L index from the time of surgery to 12 months postoperatively compared to the established Danish reference norms [40], are presented in Figure 4-3. Twelve months postoperatively, only males in the study population reported "worse" compared to the established Danish reference population norms due to none overlapping 95% CI.

The mixed-model RM-ANOVA of the Eq5d-5L indexes showed a substantial main effect for time (RM-MX-ANOVA: $F_{3,136}$ =23.5, P<0.001) with both genders showing a significant increase in the Eq5d-5L index between the 6-week and the 12-month time points. The post-hoc test showed an increase in the Eq5d-5L index between all the time points, apart from 6 to 12-months postoperatively (P<0.007).

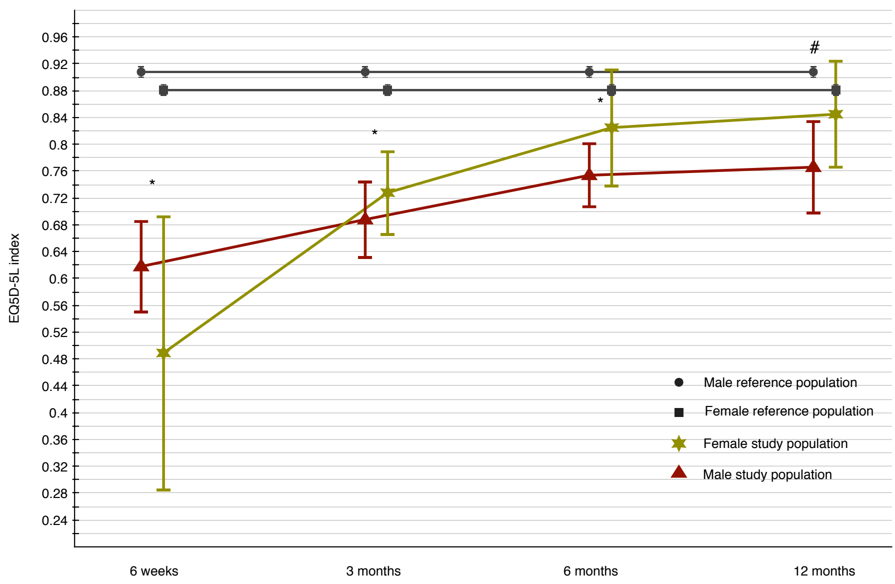

Figure 4-3: The development in Eq5d-5L index (mean, 95%CI) at the time point 6 week, 3, 6 and 12 month postoperatively divided into males and females. Reference population norms (mean, 95% CI) divided into males and females [40]. Twelve months postoperatively only males in the study population reported "worse" compared to the established Danish reference population norms due to non–overlapping 95% CI, #. The mixed-model RM-ANOVA of the Eq5d-5L indexes showed a substantial main effect for time (P<0.001) with both genders showing a significant increase in the Eq5d-5L index between the 6-week and the 12-month time points. The post-hoc test showed an increase in the Eq5d-5L index between all time points, apart from 6 to 12-months postoperatively (,P<0.007).*

At 12 months postoperatively, the mean KOOS scores for the five subscales were: Pain 85.8 (95% CI: 80.6–90.9), symptoms 88.0 (95% CI: 83.7–92.4), ADL 87.1 (95% CI: 81.9–92.3), sports 60.1 (95% CI: 50.0–70.2) and QOL 66.3 (95% CI: 58.0–74.6). Compared with an established KOOS reference population [42], the study population showed statistically, significantly worse KOOS outcomes for two (QOL, Sport) of the five subscales.

A mixed-model RM-ANOVA showed a significant main effect for time in the KOOS subscales Pain, ADL, Sports, and QOL (RM-MX-ANOVA: $F_{3,136} > 10.1$, $P<0.001$) with both genders showing a significant increase between the 6-week and the 12-month time points. The post-hoc test showed an increase in the subscale Pain between the 6-week and the 3-month (P=0.009), 6- month (P=0.006) and 12-month ($P<0.001$). For the subscale ADL and Sport the post-hoc tests showed an increase between week 6 and the 3, 6 and 12-month ($P<0.001$) and between 3 and 12-month ($P<0.001$). The subscale QOL shows an increase between 6-week and the 12-month ($P<0.001$).

Isometric muscle strength

The development in muscle strength for knee flexion and knee extension during the 12-month observation period is presented in Figures 4-4 and 4-5.

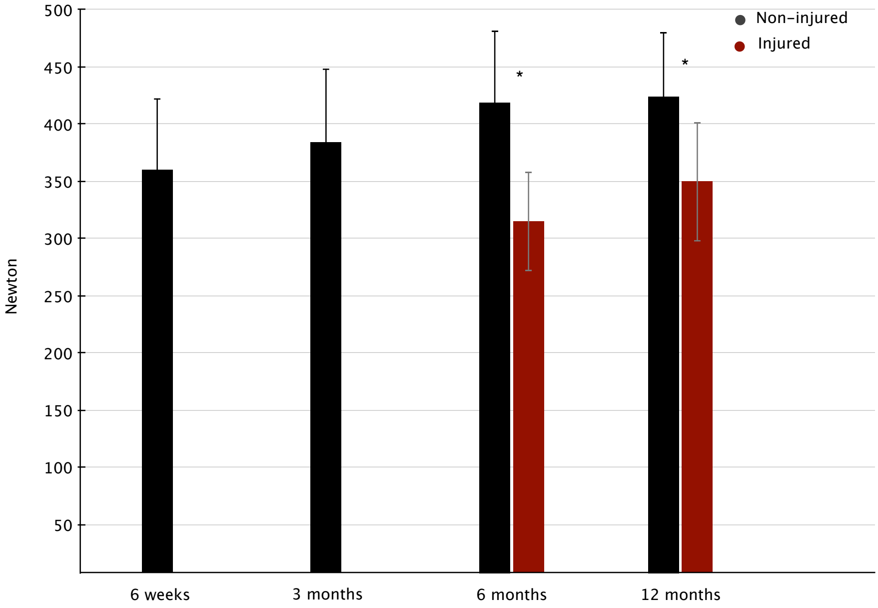

Figure 4-4: The development in muscle strength for knee extension (mean, 95% CI) at the time point 6 week, 3, 6 and 12 month postoperatively for the non-injured leg, and at time points 6 and 12 months for the injured leg.
The RM-MX-ANOVA of the time points 6 and 12 months after surgery and muscle strength between injured and non-injured leg showed significantly decreased muscle strength in the injured leg compared to the non-injured at both time points (,P<0.001).*

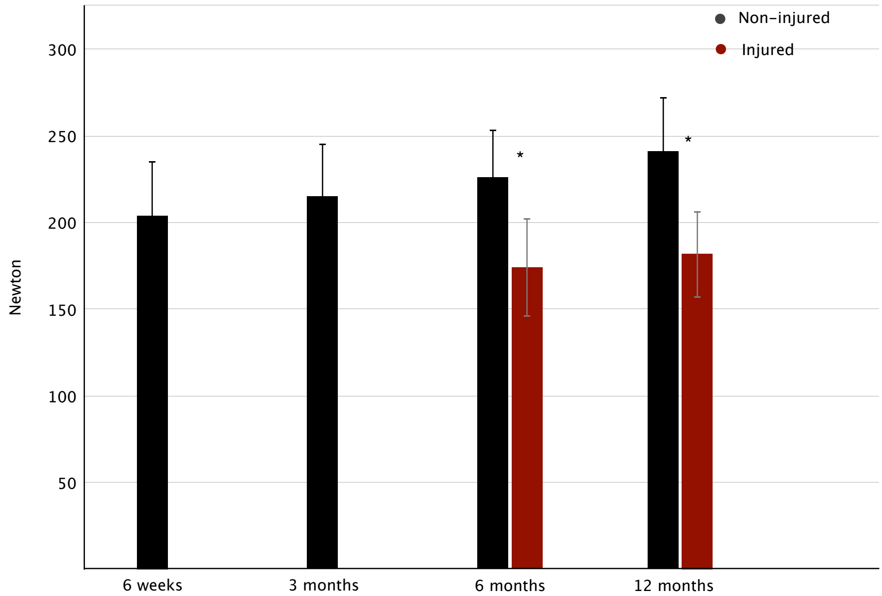

Figure 4-5: The development in muscle strength for knee flexion (mean, 95% CI) at the time point 6 weeks, 3, 6 and 12 months postoperatively for the non-injured leg, and at time points 6 and 12 months for the injured leg.
The RM-MX-ANOVA of the time points 6 and 12 months after surgery and muscle strength between injured and non-injured leg showed significantly decreased muscle strength in the injured leg compared to the non-injured at both time points (,P<0.001).*

Non-injured leg
The mixed-model RM-ANOVA showed a significant main effect for time in the non-injured leg for knee extension (RM-MX-ANOVA: $F_{3,136}$ =3.19, P=0.03) and knee flexion (RM-MX-ANOVA: $F_{3,136}$ =5.1, P<0.03) showing an increase in muscle strength between the 6-week and the 12-month time points. The analysis showed a significant between subjects effect between genders in knee extension (RM-MX_ANOVA: $F_{1,43}$ =39.5, P<0.001) and knee flexion (RM-MX-ANOVA: $F_{1,43}$ =61.1, P<0.001), showing an overall greater muscle strength in males compared to females. The post-hoc test showed a progressive increase in knee extension and flexion strength from 6 weeks to 6 and 12 months (P<0.05). Between genders the post-hoc test showed a significant difference in the increase in muscle strength favouring males. (Knee extension: mean diff. 242.4N, P<0.001, knee flexion: mean diff. 139.2N, P<0.001).

Injured leg
The mixed-model RM-ANOVA showed a significant main effect for time in the

injured leg for knee extension (RM-MX-ANOVA: $F_{1,43}$ =4.2, P=0.04) showing an increase in muscle strength between the 6-month and the 12-month time points. The analysis showed a significant between subjects effect between genders in knee extension (RM-MX-ANOVA: $F_{1,43}$ =31.7, P<0.001) and knee flexion (RM-MX-ANOVA: $F_{1,43}$ =17.7, P<0.001) showing an overall greater muscle strength in males compared to females. The post-hoc test showed a significantly progressive increase in the muscle strength between the 6-month and 12-month time points for knee extension. Between genders, the post-hoc test showed a significant difference in the increase in muscle strength favouring males. (Knee extension: mean diff. 193.8N, P<0.001, knee flexion: mean diff. 91.5N, P<0.001).

Injured vs. non-injured leg.
The RM-MX-ANOVA of the time points 6 and 12 months after surgery and muscle strength between injured and non-injured leg showed a significant effect for difference between legs for knee extension (RM-MX-ANOVA: $F_{1,43}$ =45.6, P<0.001 and knee flexion (RM-MX_ANOVA: $F_{1,43}$ =32.1, P<0.001). The post-hoc test showed significantly decreased muscle strength in the injured leg compared to the non-injured (P<0.001). (Knee extension: mean diff. 89.4N, P<0.001, knee flexion: mean diff. 61.6N, P<0.001).

Functional performance outcome
Twelve months after surgery, the mean number of standings for the 30-second chair-to-stand test was 23.7 (10.0SD) with a range from 10 to 48. The development in the 30-second chair-to-stand test from surgery to the final follow–up at 12-months postoperatively is presented in Figure 4-6.

A mixed-model RM-ANOVA showed a significant main effect for time in 30-seconds chair-to-stand-test (RM-MX-ANOVA: $F_{3,136}$ =71.2, P<0.001) with both genders showing a significant increase between the 6-week and the 12-month time points. The post-hoc test showed a progressive increase in the number of standing between all the time points (P<0.001).

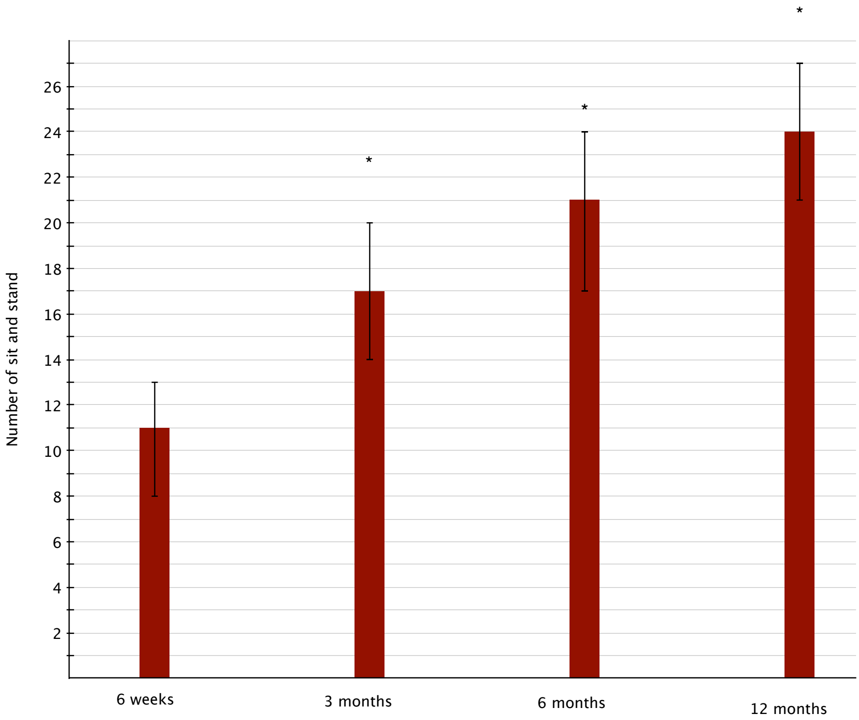

Figure 4-6: The development in functional performance (mean, 95% CI) at the time point 6 weeks, 3, 6 and 12 months postoperatively. A mixed-model ANOVA showed a significant main effect for time in 30-seconds chair-to-stand-test (P<0.001) with both genders showing a significant increase between the 6-week and the 12-month time points. The post-hoc test showed a progressive increase in the number of standing between all the time points (, P<0.001).*

Analysis of variables affecting patient reported outcomes.

Twelve months after surgery, an increasing difference in muscle strength between the injured and the non-injured leg for knee extension and high-energy trauma were associated with worse Eq5d-5L outcome scores (P<0.006). Six months postoperatively, the analyses show no statistically significant association between any of the variables.

CHAPTER 5. DISCUSSION

5.1. MAIN FINDINGS

The aim of the present PhD thesis was to report up-to-date information on the epidemiology of tibial shaft fractures and to investigate the development in quality of life, pain and functional outcomes from surgery and onwards, following tibial shaft fractures treated with intramedullary nailing. Study I reported an incidence of 16.9/100,000/year from a complete population. Study III suggested that localised, distal and bilateral hyperalgesia are common within the first 12 months following a tibial shaft fracture. Study IV reported that patients achieved a level of QOL close to a Danish reference population within the first 12 months postoperatively, and that increasing difference in muscle strength (knee extension) between the legs was associated with a decreasing QOL. Moreover, a knee injury specific questionnaire (KOOS) showed significantly worse outcome score in 2 of 5 subscales compared to a reference population at the time point 12 months postoperatively. Study II showed that with a mean of approximately 8 years follow-up, patients reported significantly worse outcomes in 4 of the 5 KOOS subscales. This was mainly evident among the younger participants. Furthermore, the KOOS scores of the five subscales were almost identical between the study populations of study II (long-term follow-up) and study IV (12-month follow-up), indicating that the level of KOOS scores reached after 12 months postoperatively is comparable to a level achieved at a mean of approximately 8 years after surgery.

5.2. INCIDENCE

Study I provided up-to-date information concerning the incidence of tibial shaft fractures and was the first to report population-based incidence from a complete population that includes almost 100% of all tibial shaft fractures in the study period. The overall incidence was 16.9/100,000/year in 2009 and 2010 combined in the North Denmark region. This was lower than an incidence reported by Court-Brown et al. [7] (2006), who reported an incidence of 22.0/100,000/year in the United Kingdom. In contrast to Court-Brown et al. [7], this study includes all fractures despite age and has a complete population size. A Swedish study conducted between 1998 and 2004 reported an incidence of 17.0/100,000/year [8]. This is comparable to the findings in the present study conducted in 2009 to 2010. Weiss et al. [8] reported a decreasing incidence from 18.7/100,000/year in 1998 to 16.1/100,000/year in 2004. A continuous decrease in incidence would result in an expected incidence in 2009 and 2010 considerably lower than 16.1/100,000/year in 2004. This is in contrast to 16.9/100,000/year found in the present study.

5.3. PATIENT-REPORTED OUTCOMES

Study IV reported the development in ***short-term*** patient-reported QOL. In the 12-month observation period, the QOL increased with time, and the patients achieved a level of QOL below but close to the established Danish reference population. Twelve months postoperatively, only male patients reported worse QOL compared to the established Danish reference norms. These findings are supported by Skoog et al. [24] who reported that patients with tibial shaft fractures had not recovered fully to the pre-injury QOL neither 4- nor 12-months postoperatively, according to the SF-36 questionnaire. Moreover, study IV showed a significantly worse outcome in two of the five KOOS subscales compared to the reference population [42] at 12-months follow-up.

Study II reported the ***long-term*** patient-reported outcomes following a tibial shaft fracture and showed that approximately 8 years after the fracture patients reported significantly worse outcomes for four of the five KOOS subscales compared to the reference population. This was mainly evident among the younger participants. These findings are supported by a number of studies, all reporting some limitations in the patient-reported outcomes at long-term follow up following a tibial shaft fracture [3,6,17-20,22-25,31-37]. In contrast, Lefaivre et al. [3] reported a comparable level of function compared to an established population norm, according to the SF-36 questionnaire with 14 years of follow-up. Connelly et al [27] reported a good overall long-term functional outcome measured with the SF-12 questionnaire at 12 to 22 years postoperatively.

The understanding of QOL and functional performance following a tibial shaft fracture is contradictory. Outcomes from the present PhD thesis suggested that the significantly worse level of the knee injury specific score (KOOS) achieved 12 months post-surgery is comparable to the KOOS level achieved at a mean of approximately 8 years after surgery.

This suggests that generic questionnaires such as SF-36, SF-12 and Eq5d-5L evaluating QOL are less sensitive compared to an injury specific questionnaire (KOOS) in capturing disabilities following a tibial shaft fracture. This might indicate that both generic and injury specific questionnaires are required in evaluating outcome following tibial shaft fractures.

5.4. PAIN

Knee pain is reported as a common complication following intramedullary nailing of a tibial shaft fracture [7,17,18]. Study III was the first study to systematically examine pain reaction and hyperalgesia in patients following a tibial shaft fracture treated with intramedullary nailing, from the time of surgery until 12 months after the fracture. The main outcome of this study was the observation of progressively increasing PPT levels at all sites (1–6), and reduced PPTs at the injured leg compared to the non-injured leg, and a bilateral equal level of mechanical pain pressure within 12 months.

The change in PPTs in both the injured and non-injured leg in the observational period found in this study may indicate that localised, distal and bilateral widespread hyperalgesia after tibial shaft fractures is common, although no conclusion can be drawn in the absence of a pre-injury level of PPTs. Moreover, no changes were observed for the PPTs measured at the forearm, suggesting that the possible presence of distal and widespread hyperalgesia in the lower extremity was not part of a generalised sensitisation in the patient group. No other studies have systematically evaluated pain reactions from the time of surgery and onwards, following a tibial shaft fracture.

This thesis suggests that not only is knee pain a common complication after tibial shaft fractures but also a combination of localised, distal and bilateral widespread hyperalgesia is common within the first 12 months postoperatively.

The observed increase in PPTs during the 12 months in both legs may be explained by lower PPTs after injury, which is becoming normalised. But as no data from healthy participants are included, no unequivocal conclusion can be drawn on the causality. In agreement with the findings of the present study, previous studies evaluating other musculoskeletal disorders have reported bilateral decreased PPT levels and widespread hyperalgesia [52]. The reason for these findings may be a central segmental sensitisation or alternatively simple overuse in the non-injured leg, but no studies have demonstrated this.

The study did not show correlations between VAS and PPT levels, indicating that increased hyperalgesia was not associated with increased pain following a fracture of the tibia. However, Arendt-Nielsen et al. [53] reported statistically significant correlations between individual VAS pain and PPTs in patients with painful knee osteoarthritis. This difference may be due to the relatively short time period and acute onset of pain following an injury such as a fracture of the tibia. Patients with knee osteoarthritis present with chronic and progressive disability and, as a consequence, pain, which has often been present for a considerable amount of time. Furthermore, the present study population present with generally low VAS scores compared to degenerative deceases such as osteoarthritis were higher VAS pain scores, are commonly reported [53,54].

5.5. MUSCLE STRENGTH

Study IV provides information concerning the development in muscle strength from surgery to 12 months postoperatively and showed that patients demonstrated significantly progressive increasing muscle strength in the contralateral leg from the time of surgery and onwards. Between genders, the study showed a significant difference in the increase in muscle strength favouring males in both the injured and non-injured leg. The injured leg of the patients demonstrated decreased muscle strength compared to the non-injured leg for knee extension and knee flexion 6 and 12 months after surgery. Moreover, patients demonstrated significantly progressive increasing functional performance from the time of surgery and onwards. Several other studies have reported decreased muscle strength and function after tibial fractures [19,20,26,29,30]. Most studies are retrospective in design, including patients treated with various operative techniques, and no recent studies have compared the muscle strength to the patient-reported QOL. In a prospective study, Gaston et al. [30] reported that two weeks after a tibial fracture, the knee flexor and extensor muscles are reduced to about 40% of normal power, which increases to between 75% and 85% after one year. Gaston et al. [30] did not compare the decreased muscle force to patient-reported function, difference in muscle function between legs, genders or patient-reported QOL. Moreover, Väistö et al. [19,26] reported, with a long-term (3.2 and 8.1 years) follow-up, a decreased muscle force for knee extension and flexion in the injured leg. This was especially pronounced for knee extension and for patients with knee pain. Patients in the studies of Väiströ et al. [19,26] with no knee pain reported an almost balanced muscle function between the two legs after both 3.2 and 8.1 years postoperatively. Henriksen et al. [55] showed a significant inhibition of muscle strength for knee flexion and knee extension in healthy volunteers followed by experimental knee pain, and that muscle strength was positively correlated to the pain intensity. However, it is commonly known that reduced use of the lower limb leads to atrophy of the muscles resulting in decreased muscle strength [56]. Unfortunately the present study has no information regarding muscle atrophy. Moreover, it is documented that knee swelling influences the muscle strength of knee extension and knee flexion [57]. The study has no collected data regarding knee swelling, which is known as a common problem following intramedullary nailing of the tibia [3]. Findings indicate that it takes considerable time to regain muscle function and balanced muscle strength between the injured and non-injured leg after a fracture of the tibial shaft, but the aetiology has not yet been satisfactorily established, and more research is needed. Focus on muscle function in physiotherapy and postoperative rehabilitation may be important.

5.6. ASSOCIATION BETWEEN QOL AND MUSCLE STRENGTH

Study IV is the first to systematically evaluate the association between the development in QOL and the difference in muscle strength between the injured and non-injured leg at the time point 6- and 12 months postoperatively. An increasing difference in muscle strength for knee extension was associated with a statistically significant decreasing QOL at 12 months postoperative. No significant association between decreased muscle strength for knee flexion and QOL was observed. These findings are novel. Moreover, the association between increasing difference in muscle strength and worse QOL are supported by Larsen et al. [51] from a recent publication of intramedullary nailing of femoral shaft fractures.

5.7. STRENGTHS AND LIMITATIONS

The strength of study I is that Denmark has a unique opportunity to do population-based studies. All patient contacts with hospitals and clinics in Denmark are registered in the Danish National Patient Register (DNPR) [58] and is required by law. The Central Person Register (CPR) number is given to all residents of Denmark and is registered in the Civil Registration System. Hospital identification, date and time of activity, and patient's municipality (among other characteristics) are registered [59]. This system enables a complete registration of all health related issues on an individual and population based level. The limitation of study I is potentially missing registrations, due to the retrospective design, and this may be a bias. Furthermore, some problems related to error in relation to the classification of the fractures, and hence, the coding in the DNPR, might be present, which would represent a bias.

The limitations of studies II, III and IV are that they are all observational studies (cross-sectional design and prospective follow-up studies), implying that no conclusions regarding causality can be drawn from these studies. However, all three studies provided novel findings and useful, clinically relevant hypothesis generating information, relevant for future clinical trials.

Another strength of studies II and III was the prospective study design and a high response rate throughout the 12-month study period in both studies. Study IV was conducted on 294 patient with up to 13 years follow-up time. A response rate of 76% and 24% non-responders may be a bias.

The present thesis uses several different measures to capture different aspects of the outcome following a tibial shaft fracture. The reliability of the selected outcome measures were not tested in the present thesis, or previously for patients with a tibial shaft fracture treated with intramedullary nailing. This may be a bias. However, all measures used in the present thesis is commonly used and validated on other lower limb orthopaedic diagnoses.

A further limitation is a lack of power in study IV regarding the KOOS score. The power calculation was based on the main outcome score (Eq5d-5L), and with an observed large variance of the KOOS scores, this variable was slightly underpowered.

Another strength of this thesis is the existence of the KOOS and Eq5d-5L reference populations. Reference populations offer a unique opportunity to evaluate the outcome of a group of patients compared to the general population. Moreover, we anticipated that the present study population would not present an increased degree of comorbidity or other disability, compared to the general population, which implies that the reference populations would be useful in comparison. The reference population of KOOS was conducted in southern Sweden and whether this is a comparable group is arguable, which implies that this may be a bias.

Finally, all but study I is based on a study population from a single centre, which may be the foundation for a potential selection bias indicating that extrapolation on the conclusions of these studies may be biased.

CHAPTER 6. CONCLUSION

This PhD thesis reported an incidence of tibial shaft fractures at 16.9/100,000/year on a complete Danish regional population.

The results of this thesis suggested that regaining pre injured QOL and muscle strength following a tibial shaft fracture takes considerable time. The PhD thesis demonstrated that patients following a tibial shaft fracture treated with intramedullary nailing within the first year postoperatively achieved a level of patient-reported QOL below but close to a reference population. Despite a high level of patient-reported QOL within the first year postoperatively, an injury specific questionnaire (KOOS) showed a worse outcome score compared to a reference population after both 12 months and approximately 8 years after surgery. This indicates that the level of disability at 12 months after surgery is persistent throughout the following years. Whether or not the individual disability level 12 months after surgery is predictive of the following years, will need further research. Both a generic and an injury specific questionnaire may be required in evaluating outcomes following a tibial shaft fracture.

Within the first year postoperatively patients demonstrated persistent, decreased muscle strength for knee extension and knee flexion in the injured leg compared to the non-injured leg. The increasing difference in muscle strength between the injured and non-injured leg for knee extension was associated with a significant decreasing QOL.

Furthermore, the results suggested that localised, distal and bilateral widespread hyperalgesia was common during the first year after a tibial shaft fracture treated with intramedullary nailing, but the observed hyperalgesia was not part of a generalised sensitisation in the patient group.

CHAPTER 7. CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

This PhD thesis outlines a number of issues that could be the basis of further studies and future clinical interest. First of all, the understanding of the development in patient-reported QOL and injury specific outcome lacks evidence. Large-scale prospective follow-up studies are needed to understand the development in the patient reported QOL and injury specific outcome, and the relationship between them.

Moreover, the observed persistent, decreased muscle function in the injured leg compared to the non-injured leg is of clinical interest. Of even more interest is the reported significant association between increased difference in muscle strength for knee extension and worse QOL, within the first year after fracture. To investigate whether muscle strength training can improve patient-reported QOL, randomised controlled trials are needed.

Furthermore, findings from the present study suggested that localised and bilateral hyperalgesia after tibial shaft fractures are common within the first 12 months after surgery, and clinicians should take this information into consideration when planning rehabilitation programs.

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APPENDICESREFERENCES

Appendix A. Paper I: Incidence and epidemiology of tibial shaft fractures.

Appendix B: Paper II: Restrictions in Quality of Life after Intramedullary Nailing of Tibial Shaft Fracture. A retrospective follow-up study of 223 cases.

Appendix C: Paper III: Local and widespread hyperalgesia after isolated tibial shaft fractures treated with intramedullary nailing.

Appendix D: Paper IV: Decreased muscle strength is persistent and associated with worse Quality of Life one year after intramedullary nailing of a tibial shaft fracture. A prospectively observational study of 49 patients with 12 months follow-up.

SUMMARY

The overall purpose of the present PhD thesis was to provide up-to-date information of the epidemiology of tibial shaft fractures and to investigate the development in quality of life, pain and functional outcomes from surgery and onwards, following a tibial shaft fracture treated with intramedullary nailing.

Study I reported an incidence of 16.9/100,000/year from a complete population. Study II reported the long-term patient-reported outcomes and showed that approximately 8 years after the fracture patients reported significantly worse outcome for 4 of the 5 KOOS subscales compared to the reference population. Study III suggested that localized, distal and bilateral hyperalgesia are common within the first 12 months postoperatively. Study IV reported that patients achieved a level of QOL close to an established reference population within the first 12 months postoperatively. However, study IV also showed a significant worse outcome in 3 of the 5 KOOS subscales compared to a reference population at 12-months follow-up. Moreover, this study showed that increasing difference in muscle strength for knee extension between legs was associated with a decreasing QOL.

The results of this thesis suggested that regaining pre injured QOL and muscle strength following a tibial shaft fracture takes considerable time.

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