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a prospective 1-year follow-up cohort study

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Abstract:	Introduction: To evaluate the development in patient-reported quality of life (QOL) and muscle strength in the period from surgery to 12 months postoperatively after intramedullary nailing of a tibial shaft fracture. Material and Methods: The design was a prospective, follow-up cohort study. QOL was measured with the questionnaire Eq5d-5L and compared to norm data from a reference population. Recordings of pain and contralateral muscle strength (isometric maximal voluntary contraction (MVC) for knee flexion and extension were collected at 6 weeks, 3, 6, and 12 months postoperatively. Ipsilateral MVCs were recorded at 6 and 12 months. Results: Forty-nine patients were included. The mean age at the time of fracture was 43.1 years (18 to 79 years). Twelve months postoperatively, the mean Eq5d-5L index was 0.792 (95%CI: 0.747-0.837). Throughout the 12 months postoperatively, patients reported worse QOL compared to the reference population. Six and twelve months after surgery patients demonstrated decreased muscle strength in the injured leg compared to the non-injured leg for knee extension and flexion ($P<0.001$). Twelve months postoperatively, increasing relative difference in muscle strength during knee extension show a fair correlation to worse QOL ($R=0.541$, $P<0.001$). Conclusions: Throughout the 12 months postoperatively, patients reported worse QOL compared to the reference population. Muscle strength in the non-injured leg improved over time and was higher after 6 and 12 month compared with the injured leg.

Decreased QOL and muscle strength are persistent one year after intramedullary nailing of a tibial shaft fracture – a prospective one-year follow-up cohort study

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ABSTRACT

Introduction: To evaluate the development in patient-reported quality of life (QOL) and muscle strength in the period from surgery to 12 months postoperatively after intramedullary nailing of a tibial shaft fracture.

Material and Methods: The design was a prospective, follow-up cohort study. QOL was measured with the questionnaire Eq5d-5L and compared to norm data from a reference population. Recordings of pain and contralateral muscle strength (isometric maximal voluntary contraction (MVC) for knee flexion and extension were collected at 6 weeks, 3, 6, and 12 months postoperatively. Ipsilateral MVCs were recorded at 6 and 12 months.

Results: Forty-nine patients were included. The mean age at the time of fracture was 43.1 years (18 to 79 years). Twelve months postoperatively, the mean Eq5d-5L index was 0.792 (95%CI: 0.747–0.837). Throughout the 12 months postoperatively, patients reported worse QOL compared to the reference population. Six and twelve months after surgery patients demonstrated decreased muscle strength in the injured leg compared to the non-injured leg for knee extension and flexion ($P<0.001$). Twelve months postoperatively, increasing relative difference in muscle strength during knee extension show a fair correlation to worse QOL ($R=0.541$, $P<0.001$).

Conclusions: Throughout the 12 months postoperatively, patients reported worse QOL compared to the reference population. Muscle strength in the non-injured leg improved over time and was higher after 6 and 12 month compared with the injured leg.

***Keywords**: intramedullary nailing, tibia shaft fracture, QOL, muscle strength*

INTRODUCTION

During the last decades, intramedullary nailing has been the standard treatment method in the treatment of tibia shaft fractures [1-3]. A recent study reported the incidence of tibial shaft fractures to be 16.9/100,000/year [4] representing around 40% of all long-bone fractures in adults [5].

Several studies report the functional and radiological long-term outcome after intramedullary nailing of tibial shaft fractures. Knee and ankle pain, joint stiffness, degenerative joint disease, rotational malalignment, complications due to soft tissue injury, muscle weakness, and limitations in activity of daily living and quality of life (QOL) are commonly reported [6-22]. A study by Skoog et al. [19] reports that patients with tibial shaft fractures had not recovered to their pre-injury QOL, neither at four nor at twelve months postoperatively. However, there is a lack of prospective studies evaluating the development in short-term outcomes from the time of surgery and onwards. This information are especially important for clinicians when advising patients on development in QOL and muscle strength following a fracture of the tibia.

Several studies have reported decreased muscle strength following a tibial fracture [20,22-25]. To the authors knowledge no studies have described the association between the development in muscle strength postoperatively and the short-term patient-reported QOL and pain following a tibial shaft fracture. A recent study by Larsen et al. [26] reported a significant association between decreased muscle strength and worse patient-reported outcomes in patients following a femoral shaft fracture treated with intramedullary nailing.

The objective of the present study was to evaluate the development in patient-reported QOL and muscle strength in a period from surgery to 12 months postoperatively after intramedullary nailing of a tibial shaft fracture. The explorative aim was to report the association between muscle strength, pain and QOL at 6 and 12 months postoperatively

following intramedullary nailing of a tibial shaft fracture.

The primary hypothesis was that patients would report worse patient-reported QOL compared to an established reference-population in a period from 6 weeks to 12 months postoperatively. Moreover, the hypothesis was that patients would show impaired muscle strength in the injured leg compared to the non-injured leg in a period from 6 weeks to 12 months postoperatively.

PATIENTS AND METHODS

Study design

The study design was a prospective cohort follow-up study including all patients treated with intramedullary nailing after a tibial shaft fracture, between September 2012 and June 2014 at Aalborg University Hospital, Denmark. Patients below 18 years of age were excluded. Patients with multi-trauma, bilateral fractures and patients with pathological fractures were excluded. Patients who were unable to fill out the questionnaires due to mental disabilities were excluded.

Basic characteristics regarding age, gender, body mass index (BMI), trauma mechanism, type of trauma, fracture classification were obtained at the time of admission to hospital where participants also gave written informed consent. Complications were reported throughout the study. All patients were systematically examined at the outpatient clinic at 6 weeks, and at 3, 6 and 12 months postoperatively.

The primary outcome measurement of this study was the development in patient-reported QOL (Eq5d-5L index) from 6 weeks to 12 months after surgery. The secondary outcome measurements were the development in muscle strength (knee flexion and extension), 30-seconds chair-to-stand test, knee pain and the Knee Injury and Osteoarthritis Outcome

Score (KOOS). Moreover, radiological evaluation regarding union and malalignment were obtained.

The Danish Data Protection Agency (J. nr. 2008-58-0028) and the local ethics committee (J.nr: N-201-200-11) approved the study, which was performed according to the principles of the Helsinki declaration. The reporting of the study complies with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement [27].

Patient reported measurements

Eq5D-5L is a standardized and validated instrument to assess health outcome [28]. It consists of five dimensions: Mobility, self-care, usual activities, pain/discomfort and 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'. An Eq5D-5L index at 1.0 indicated full health, and -0.59 denoted death. Eq5d reference data form a general population-based sample in Denmark is available [30].

The Knee Injury and Osteoarthritis Outcome Score (KOOS) [31] is a standardized and validated instrument to evaluate knee and associated problems. The questionnaire includes 5 subscales. A total score of 100 indicate no symptoms, and 0 indicate major symptoms. KOOS reference data [32] from a general population-based sample in southern Sweden is available.

Assessments of objective measurements

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. The patients were asked to perform an isometric 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. [33].

Functional performance was assessed by the 30-seconds chair-to-stand test. The patients were asked to rise 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 up was the outcome measure [34].

Pain

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

Radiological measurements

Fracture classification was performed according to the AO classification [35] and was conducted on preoperatively obtained X-rays. Postoperatively, X-rays of the fractured lower leg wereas obtained and used to evaluate the bone healing and alignment. The radiological assessments were made on AP and side X-rays.

The evaluation of bone 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 1 of 4 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 evaluation union after tibial fractures [36].

Statistics

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

A two-way mixed repeated measures analysis of variance (ANOVA) was used to analyze the development in Eq5d-5L index, KOOS, MVC, chair-to-stand test and pain 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.

At 6 and 12 months postoperatively a Spearman's rank test was used for analysis of the correlation between QOL, VAS pain and relative difference in muscle strength between the injured and non-injured leg.

A P-value of < 0.05 was considered significant. The statistical analysis was performed by SPSS (version 22).

RESULTS

A total of 50 patients were treated for a tibial shaft fracture with intramedullary nailing during the study period. One patient was initially excluded due to a pathological fracture. Thus, the study population consists of 17 females and 32 males. The mean age at the time of the fracture was 43.1 years, ranging from 18 to 79 years. The baseline characteristics of all patients are presented in Table 1.

Throughout the study period 5 patients were lost to follow-up. One patient was excluded between the 3 and the 6-month follow-up due to a tibial fracture of the opposite lower leg, and two patients refused to enter the study after the 3-month follow-up. One patient

158 died and one patient was diagnosed with a mental disability between the 6 and the 12-month
159 follow-up.
160
161 *Patient reported outcome*
162 Twelve months postoperatively the mean Eq5d-5L index was 0.792 (95%CI: 0.747–0.837).
163 The mean Eq5d-5L VAS was 84.6 (95%CI: 80.3–88.9). The mean Eq5d-5L index from the
164 time of surgery to 12 months postoperatively compared to the age matched Danish reference
165 norms [30], are presented in Figure 1. Throughout the 12 months postoperatively, patients
166 reported worse QOL compared with the age matched established Danish reference population
167 norms due to none overlapping 95%CI.
168 The mixed-model ANOVA of the Eq5d-5L indexes showed a substantial main effect
169 for time (RM-MX_ANOVA: $F_{3,136}=25.3$, $P<0.001$) showing an significant increase in the
170 Eq5d-5L index between the 6-week and the 12-month time points. The post-hoc test showed
171 an increase in the Eq5d-5L index between all the time points, apart from 6 to 12-months
172 postoperatively ($P<0.004$).
173 The KOOS score from the time of surgery to 12 months postoperatively is presented
174 in Figure 2. At 12 months postoperatively the mean KOOS scores for the five subscales were:
175 Pain 84.5 (95%CI: 79.5–89.5), symptoms 86.9 (95%CI: 82.7–91.1), ADL 86.4 (95%CI: 81.5–
176 91.3), sports 57.2 (95%CI: 47.6–66.8) and QOL 63.4 (95%CI: 55.5–71.3). Compared with an
177 established KOOS reference population [32], the study population showed statistically worse
178 KOOS outcomes for two (QOL, Sport) of the five subgroups, due to none overlapping 95%CI.
179 See Table 2.
180 A mixed-model ANOVA showed a significant main effect for time in all the five
181 KOOS subscales (RM-MX_ANOVA: $F_{3,136}>2.9$, $P<0.04$) showing a significant increase
182 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 6-months (P=0.006) and 12-month (P=0.004). For the subscale ADL and sport the post-hoc tests showed an increase between week 6 and the 3, 6 and 12-month (P<0.002) and between 3 and 12-month (P=0.001). The subscale QOL shows an increase between the 6-week and the 12-month (P=0.004).

Isometric muscle strength

The development in muscle strength from surgery to final follow up at 12 months postoperatively divided into injured and non-injured legs are presented in Figure 3a (knee-extension strength) and 3b (knee-flexion strength).

Non-injured leg: The mixed-model ANOVA showed a significant main effect for time in the non-injured leg for knee extension (RM-MX_ANOVA: $F_{3,136}$=3.0, P=0.03) and knee flexion (RM-MX_ANOVA: $F_{3,136}$=5.5, P=0.004) showing an increase in muscle strength between the 6-week and the 12-month time points. The post-hoc test showed a progressive increase in knee extension strength from 6 weeks to 6 months (P=0.03) and knee flexion strength from 6 weeks to 12 months (P=0.01).

Injured leg: The mixed-model ANOVA showed no significant main effect for time in the injured leg for knee extension and knee flexion (RM-MX_ANOVA: $F_{1,43}$<2.7, P>0.11) showing no significant increase in muscle strength between the 6- and the 12-month time points.

Injured vs. non-injured leg: The RM-ANOVA of the time points 6 and 12 months after surgery and muscle strength between the injured and non-injured leg showed a significant effect for difference between legs for knee extension (RM-MX_ANOVA: $F_{1,43}$ =49.0, P<0.001 and knee flexion (RM-MX_ANOVA: $F_{1,43}$=39.6, P<0.001). The post-hoc test showed significant decreased muscle strength in the injured leg compared to the non-injured at both time points (P<0.001).

208

209 *Functional performance outcome*

210 Twelve months after surgery, the mean number of standings for the 30-second chair-to-stand
211 test was 23.9 (9.7SD). The development in the 30-second chair-to-stand test from surgery to
212 the final follow up at 12-months postoperatively is presented in Figure 3c.

213 A mixed-model ANOVA showed a significant main effect for time in 30-seconds
214 chair-to-stand-test (RM-MX_ANOVA: $F_{3,136}$=101.2, P<0.001) showing a significant increase
215 between the 6-week and the 12-month time points. The post-hoc test showed a progressive
216 increase in the number of standing between all the time points (P<0.001).

217

218 *Pain*

219 At the final examination, 12 months after surgery, the VAS score for the worst pain during
220 the last 24 hours was reported with a range from 0 to 10 cm. Nineteen patients report a VAS
221 of 0, 16 patients reported a VAS between 1 and 5, and 9 patients reported a VAS between 6
222 and 10. The VAS score for resting pain was reported with a range from 0 to 5 cm. Eight
223 patients reported a VAS between 1 and 5, and 36 reported a VAS score of 0. Throughout the
224 12-month observational period the mean VAS score for the worst pain during the last 24
225 hours was: 6 week=3.1(2.4SD), 3 month=3.6(2.7SD), 6 month=2.6(2.5SD) and 12
226 month=2.4(2.9SD).

227 The mixed-model ANOVA showed a significant main effect for time and worst pain
228 during the last 24 hours (RM-MX_ANOVA: $F_{3,136}$=4.5, P=0.005) showing a significant
229 increase between the 6-week and the 12-month time points. The post-hoc test showed a
230 progressive decrease in VAS scores between the time points 3- and 12-month (P=0.04).

231

232 *Radiological measurements*

All fractures united during the 12-month study period (N=44, completed the final radiological examination). At the 3-month follow-up, 3 fractures presented with union, 39 with partial union and 7 fractures with no union. Six months postoperatively, 36 patients presented with union and 10 with partial union. Twelve months after surgery, two patients were out of alignment, representing a varus deformity of 7° and 9° respectively. No patients presented with flexion, extension or valgus deformity >5°.

Correlations between QOL, Pain and muscle strength (knee extension and knee flexion).

The relationship between individual VAS scores (worst pain during the last 24 hours) and the relative difference in muscle strength between legs at 6- and 12- months postoperatively showed weak correlations for both knee extension and knee flexion (Spearman's rank test: $R > 0.386$, $P < 0.01$).

The relationship between QOL (Eq5d-5L) and the relative difference in muscle strength between legs at 6 and 12 months postoperatively showed no significant correlations at 6 months but a fair correlation for knee extension at 12 months postoperatively (Spearman's rank test: $R = 0.541$, $P < 0.001$).

DISCUSSION

To our knowledge this is the first study to systematically report the short-term development in patient-reported QOL, knee function and the maximum isometric voluntary contraction strength in a period from the time of fracture to 12 months after surgery in a non-selected group of patients with isolated tibial shaft fractures, all treated with intramedullary nailing.

In the 12-months observation period, the QOL (Eq5d-5L index) increased significantly with time. Twelve months postoperatively, patients had not recovered fully, and reported worse QOL compared to the age matched established Danish reference norms.

Moreover, the study showed a significant worse outcome in two of five KOOS subscales compared to the reference population at 12-months follow-up. These findings are supported by Skoog et al. [19] reporting 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, the present findings are supported by Tay et al. [38] reporting that patients with lower limb long bone shaft fractures presented with residual patient-reported physical disability during the first year after fracture.

Patients in the present study demonstrated significantly progressive increasing muscle strength in the contralateral leg from the time of surgery and onwards. 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 [20,22-25]. 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. [24] reported that two weeks after a tibial fracture, the knee flexor and extensor muscles are reduced to about 40% of normal power, which rises to between 75% and 85% after one year. Moreover, Väistö et al. [22,25] 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. Patients in the studies of Väiströ et al. [22,25] with no knee pain reported almost a balanced muscle function between the two legs. Henriksen et al. [40] 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. The present study showing generally low level of pain and a weak correlations between increasing relative difference in muscle

strength and pain, 6 and 12 months after surgery.

This study evaluated the correlations between QOL and relative difference in muscle strength between the injured and non-injured leg following a tibial shaft fracture. The study showed a fair correlation between relative difference in muscle strength for knee extension and QOL 12 months after surgery, indicating that increasing relative difference in muscle strength was associated to worse QOL.

Findings from the present study indicate that it takes considerable time to regain muscle function and balanced muscle strength after a fracture of the tibial shaft. Focus on muscle function in physiotherapy and postoperative rehabilitation may be important. Intervention studies are needed to investigate whether rehabilitation, including muscle strength training, can improve QOL after intramedullary nailing of isolated tibial shaft fractures.

The main limitations of this study are the observational design, implying that no conclusions regarding causality can be drawn. However, the study provided novel findings and useful, clinically relevant hypothesis generating information, relevant for future clinical trials. The present study uses several different measures and analysis to capture different aspects of the outcome following a tibial shaft fracture. The high number of analysis may increase the risk of Type 1 errors. The strength of this study is the existence of the KOOS and Eq5d-5L reference populations. Reference populations offer a unique opportunity to evaluate the outcomes of patients compared to the general population. Finally, a strength of the study is the information included of the associations between QOL, pain and muscle strength, which is novel. A further limitation is the inability of the study to perform multiple analysis, due to the number of included patients in the study.

CONCLUSION

Throughout the 12 months postoperatively, patients reported worse QOL compared to the age matched Danish reference population. Muscle strength in the non-injured leg improved over time and was higher after 6 and 12 month compared with the injured leg. The findings indicate that focus on muscle function in postoperative rehabilitation may be important following a fracture of the tibial shaft.

315 **REFERENCES**

316 1. Bone LB, Sucato D, Stegemann PM, Rohrbacher BJ (1997) Displaced isolated fractures of the tibial
317 shaft treated with either a cast or intramedullary nailing. An outcome analysis of matched pairs of
318 patients. J Bone Joint Surg Am 79:1336-1341

319 2. Hooper GJ, Keddell RG, Penny ID (1991) Conservative management or closed nailing for tibial
320 shaft fractures. A randomised prospective trial. J Bone Joint Surg Br 73:83-85

321 3. Karladani AH, Granhed H, Edshage B, Jerre R, Styf J (2000) Displaced tibial shaft fractures: a
322 prospective randomized study of closed intramedullary nailing versus cast treatment in 53 patients.
323 Acta Orthop Scand 71:160-167

324 4. Larsen P, Elsoe R, Hansen SH, Graven-Nielsen T, Laessoe U, Rasmussen S (2015) Incidence and
325 epidemiology of tibial shaft fractures. Injury 46(4):746-750

326 5. Court-Brown CM, Caesar B (2006) Epidemiology of adult fractures: A review. Injury 37:691-697

327 6. Babis GC, Benetos IS, Karachalios T, Soucacos PN (2007) Eight years' clinical experience with the
328 Orthofix tibial nailing system in the treatment of tibial shaft fractures. Injury 38:227-234

329 7. Bhattacharyya T, Seng K, Nassif NA, Freedman I (2006) Knee pain after tibial nailing: the role of
330 nail prominence. Clin Orthop Relat Res 449:303-307

331 8. Butcher JL, MacKenzie EJ, Cushing B, Jurkovich G, Morris J, Burgess A et al. (1996) Long-term
332 outcomes after lower extremity trauma. J Trauma 41:4-9

333 9. Court-Brown CM (2004) Reamed intramedullary tibial nailing: an overview and analysis of 1106
334 cases. J Orthop Trauma 18:96-101

335 10. Court-Brown CM, Gustilo T, Shaw AD (1997) Knee pain after intramedullary tibial nailing: its
336 incidence, etiology, and outcome. J Orthop Trauma 11:103-105

337 11. Dogra AS, Ruiz AL, Marsh DR (2002) Late outcome of isolated tibial fractures treated by
338 intramedullary nailing: the correlation between disease-specific and generic outcome measures. J
339 Orthop Trauma 16:245-249

340 12. Ekeland A, Thoresen BO, Alho A, Strömsöe K, Folleråas G, Haukebø A (1988) Interlocking
341 intramedullary nailing in the treatment of tibial fractures. A report of 45 cases. Clin Orthop Relat Res
342 (231):205-215

343 13. Holder-Powell HM, Rutherford OM (2000) Unilateral lower-limb musculoskeletal injury: its long-
344 term effect on balance. Arch Phys Med Rehabil 81:265-268

345 14. Josten C, Marquass B, Schwarz C, Verheyden A (2010) Intramedullary nailing of proximal tibial
346 fractures : Complications and risk factors. Unfallchirurg 113:21-28

347 15. Keating JF, Orfaly R, O'Brien PJ (1997) Knee pain after tibial nailing. J Orthop Trauma 11:10-13

348 16. Lefaivre KA, Guy P, Chan H, Blachut PA (2008) Long-term follow-up of tibial shaft fractures
349 treated with intramedullary nailing. J Orthop Trauma 22:525-529

350 17. Merchant TC, Dietz FR (1989) Long-term follow-up after fractures of the tibial and fibular shafts.
351 J Bone Joint Surg Am 71:599-606

352 18. Ryan SP, Tornetta P 3rd, Dielwart C, Kaye-Krall E (2011) Knee pain correlates with union after
353 tibial nailing. J Orthop Trauma 25:731-735

354 19. Skoog A, Soderqvist A, Tornkvist H, Ponzer S (2001) One-year outcome after tibial shaft
355 fractures: results of a prospective fracture registry. J Orthop Trauma 15:210-215

356 20. Toivanen JA, Vaisto O, Kannus P, Latvala K, Honkonen SE, Järvinen MJ (2002) Anterior knee
357 pain after intramedullary nailing of fractures of the tibial shaft. A prospective, randomized study
358 comparing two different nail-insertion techniques. J Bone Joint Surg Am 84-A:580-585

359 21. Väistö O, Toivanen J, Kannus P, Järvinen M (2008) Anterior knee pain after intramedullary
360 nailing of fractures of the tibial shaft: an eight-year follow-up of a prospective, randomized study
361 comparing two different nail-insertion techniques. J Trauma 64:1511-1516

362 22. Väistö O, Toivanen J, Kannus P, Järvinen M (2007) Anterior knee pain and thigh muscle strength
363 after intramedullary nailing of a tibial shaft fracture: an 8-year follow-up of 28 consecutive cases. J
364 Orthop Trauma 21:165-171

365 23. Nyland J, Bealle DP, Kaufer H, Johnson DL (2001) Long-term quadriceps femoris functional
366 deficits following intramedullary nailing of isolated tibial fractures. Int Orthop 24:342-346

367 24. Gaston P, Will E, McQueen MM, Elton RA, Court-Brown CM (2000) Analysis of muscle function
368 in the lower limb after fracture of the diaphysis of the tibia in adults. J Bone Joint Surg Br 82:326-331

369 25. Väistö O, Toivanen J, Kannus P, Järvinen M (2004) Anterior knee pain and thigh muscle strength
370 after intramedullary nailing of tibial shaft fractures: a report of 40 consecutive cases. J Orthop Trauma
371 18:18-23

372 26. Larsen P, Elsoe R, Graven-Nielsen T, Laessoe U, Rasmussen S (2015) Decreased muscle strength
373 is associated with impaired long-term functional outcome after intramedullary nailing of femoral shaft
374 fracture. Eur J Trauma Emerg Surg 41(6):673-681

375 27. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP (2008) The
376 Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement:
377 guidelines for reporting observational studies. J Clin Epidemiol 61:344-349

378 28. Eq-5d questionnary. http://www.euroqol.org/about-eq-5d/publications/user-guide.html. ; Accessed
379 May 2012

380 29. Wittrup-Jensen KU, Lauridsen J, Gudex C, Pedersen KM (2009) Generation of a Danish TTO
381 value set for EQ-5D health states. Scand J Public Health 37:459-466

382 30. Sorensen J, Davidsen M, Gudex C, Pedersen KM, Brønnum-Hansen H (2009) Danish EQ-5D
383 population norms. Scand J Public Health 37:467-474

384 31. KOOS questionnary [KOOS web site]. Available at: http:/www.koos.nu. Accessed May, 2012

385 32. Paradowski PT, Bergman S, Sunden-Lundius A, Lohmander LS, Roos EM (2006) Knee
386 complaints vary with age and gender in the adult population. Population-based reference data for the
387 Knee injury and Osteoarthritis Outcome Score (KOOS). BMC Musculoskelet Disord 7:38

388 33. Rathleff CR, Baird WN, Olesen JL, Roos EM, Rasmussen S, Rathleff MS (2013) Hip and knee
389 strength is not affected in 12-16 year old adolescents with patellofemoral pain - a cross-sectional
390 population-based study. PLoS One 8(11):e79153

391 34. Rikli RE, Jones CJ (1999) Development and validity og functional fitness test for community-
392 residing older adults. Journal of Aging and Physical Activity 7:127-159

393 35. Marsh JL, Slongo TF, Agel J, Broderick JS, Creevey W, DeCoster TA, Prokuski L, Sirkin MS,
394 Ziran B, Henly B, Audigé L (2007) Fracture and Dislocation Classification Compendium - 2007:
395 Orthopadic Trauma Assocoation Classification, Database and Outcome Committee. J Orthop Trauma
396 (10suppl)1-133

397 36. Templeton PA, Farrar MJ, Williams HR, Bruguera J, Smith RM (2000) Complications of tibial
398 shaft soccer fractures. Injury 31:415-419

399 37. Walters SJ, Brazier JE (2005) Comparison of the minimally important difference for two health
400 state utility measures: EQ-5D and SF-6D. Qual Life Res 14:1523-1532

401 38. Tay WH, de Steiger R, Richardson M, Gruen R, Balogh ZJ (2014) Health outcomes of delayed
402 union and nonunion of femoral and tibial shaft fractures. Injury 45:1653-1658

403 39. Larsen P, Lund H, Laesoe U, Graven-Nielsen T, Rasmussen S (2014) Restrictions in Quality of
404 Life after Intramedullary Nailing of Tibial Shaft Fracture: a retrospective follow-up study of 223
405 cases. J Orthop Trauma. 28(9):507-512

406 40. Henriksen M, Rosager S, Aaboe J, Graven-Nielsen T, Bliddal H (2011) Experimental knee pain
407 reduces muscle strength. J Pain 12:460-467

408 41. Appell HJ (1990) Muscular atrophy following immobilisation. A review. Sports Med 10:42-58

409 42. McNair PJ, Marshall RN, Maguire K (1996) Swelling of the knee joint: effects of exercise on
410 quadriceps muscle strength. Arch Phys Med Rehabil 77:896-899

411

FIGURE LEGENDS AND TITLES

Figure 1: Title: The development in Eq5d-5L index. Legends: The development in Eq5d-5L index (mean, 95%CI) at the time points 6 week, 3, 6 and 12 month postoperatively compared with age matched referece population. Reference population norms (mean, 95%CI). The mixed-model ANOVA of the Eq5d-5L indexes showed a substantial main effect for time ($P<0.001$) showing an 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 (*,$P<0.004$).

Figure 2: Title: The development in KOOS subscales. Legends: The development in KOOS subscales (mean) at the time point 6 week, 3, 6 and 12 month postoperatively. A mixed-model ANOVA showed a significant main effect for time in all the 5 KOOS subscales (*, $P<0.04$). The post-hoc test showed a significant increase in the subscale Pain between the 6-week and the 6-months ($P=0.006$) and 12-month ($P=0.004$). For the subscale ADL and sport the post-hoc tests showed an increase between week 6 and the 3, 6 and 12-month ($P<0.002$) and between 3 and 12-month ($P=0.001$). The subscale QOL shows an increase between the 6-week and the 12 months ($P=0.004$).

Figure 3a: Title: The development in muscle strength for knee extension. Legends: 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 mixed-model ANOVA of the non-injured leg showed a significant increase in muscle strength between the 6-week and the 12-month time points ($P=0.03$).
The RM-ANOVA of the time points 6 and 12 months after surgery and muscle strength between injured and non-injured leg showed a significant decreased muscle strength in the injured leg compared to the non-injured at both time points (*,$P<0.001$).

Figure 3b: Title: The development in muscle strength for knee flexion. Legends: The development in muscle strength for knee flexion (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 mixed-model ANOVA of the non-injured leg showed a significant increase in muscle strength between the 6-week and the 12-month time points (P=0.004).
The RM-ANOVA of the time points 6 and 12 months after surgery and muscle strength between injured and non-injured leg showed a significant decreased muscle strength in the injured leg compared to the non-injured at both time points (*,P<0.001).

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

Table 1: Title: The baseline characteristics of all patients. No legends.

Table 2: Title: Patient-reported outcomes 12 months after intramedullary nailing. Legends: * Paradrowski PT et al. BMC Musculoskeletal disord, 2006 [33]. ** Unpublished data. Ewa Roos personal communication, Nov 13, 2012. Paradowski et al. 2006.

Figure 1

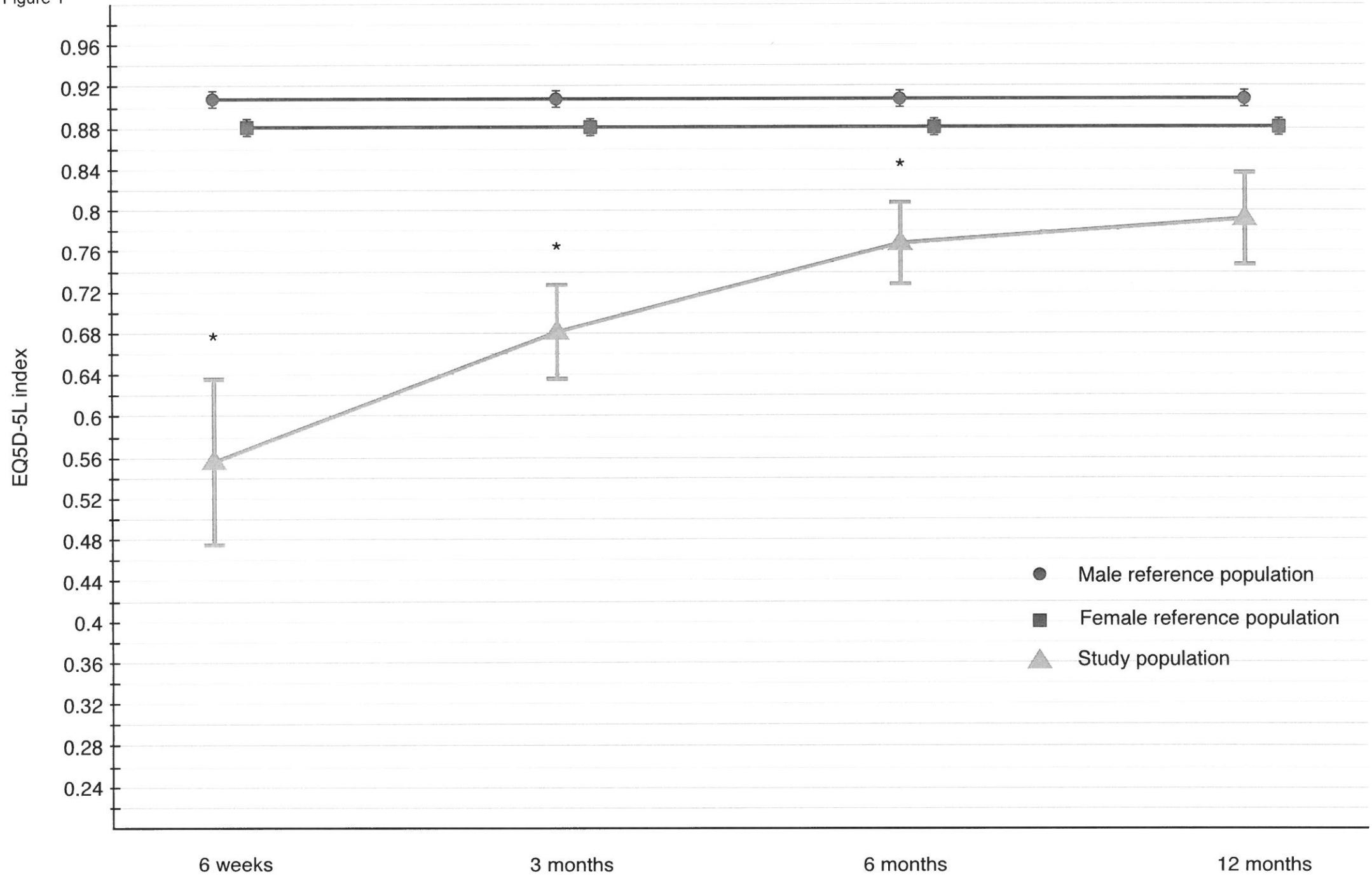
0.96
0.92
0.88
0.84
0.8
0.76
0.72
0.68
0.64
0.6
0.56
0.52
0.48
0.44
0.4
0.36
0.32
0.28
0.24
EQ5D-5L index
*
*
*
6 weeks
3 months
6 months
12 months
Male reference population
Female reference population
Study population

Figure 2

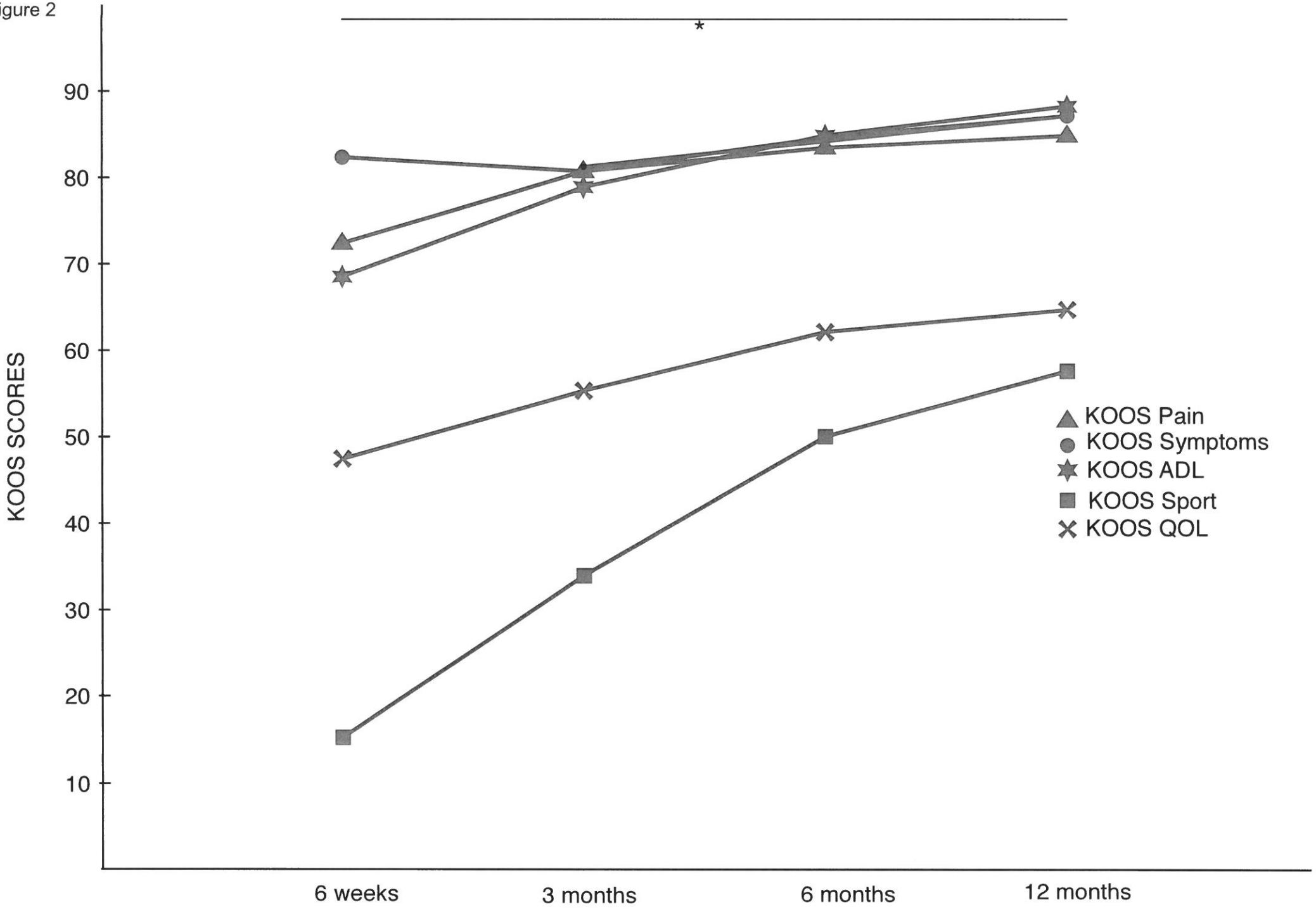
*
90
80
70
60
50
40
30
20
10
KOOS SCORES
6 weeks
3 months
6 months
12 months
KOOS Pain
KOOS Symptoms
KOOS ADL
KOOS Sport
KOOS QOL

Figure 3b

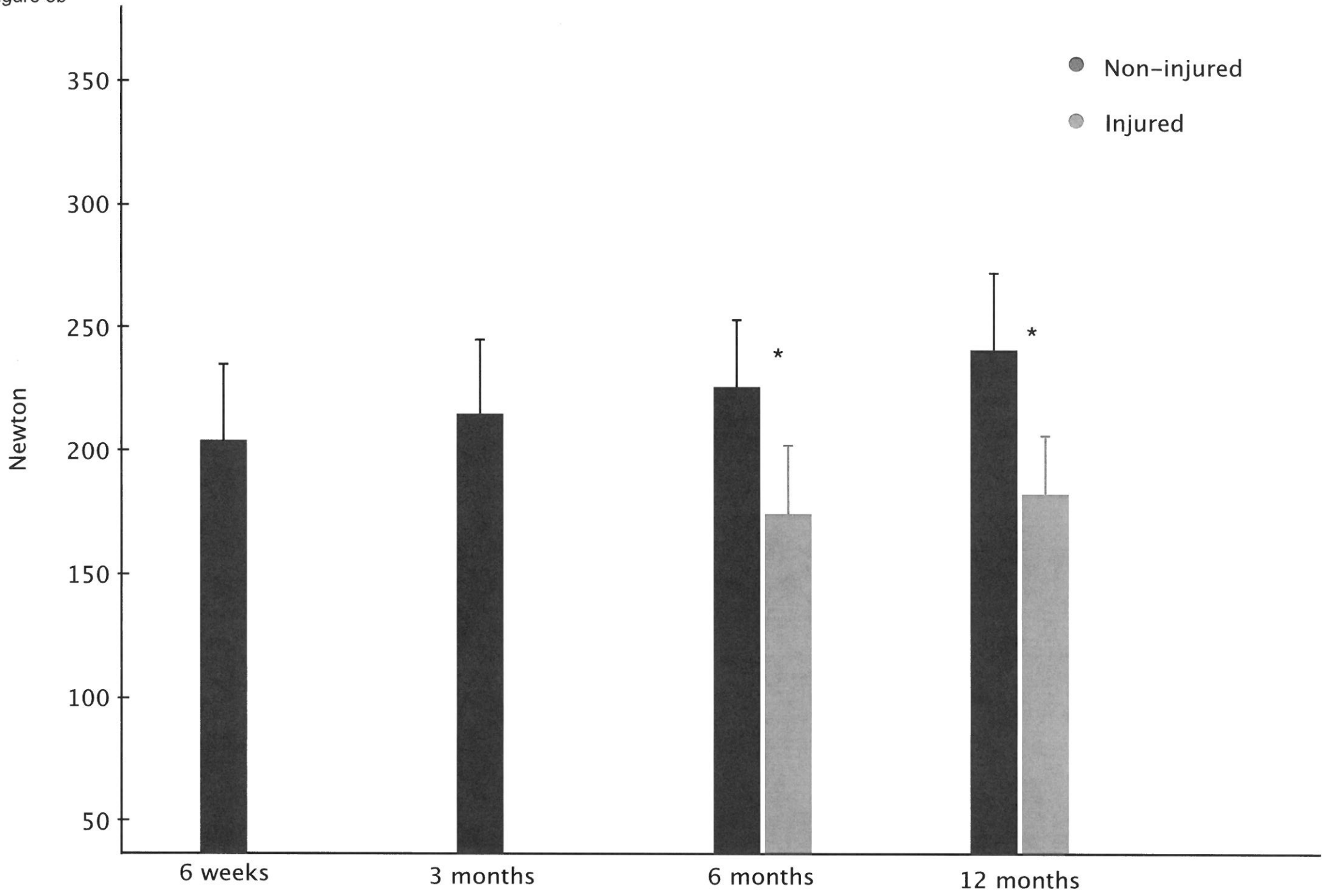
Non-injured
Injured
Newton
350
300
250
200
150
100
50
*
*
6 weeks
3 months
6 months
12 months

Figure 3a

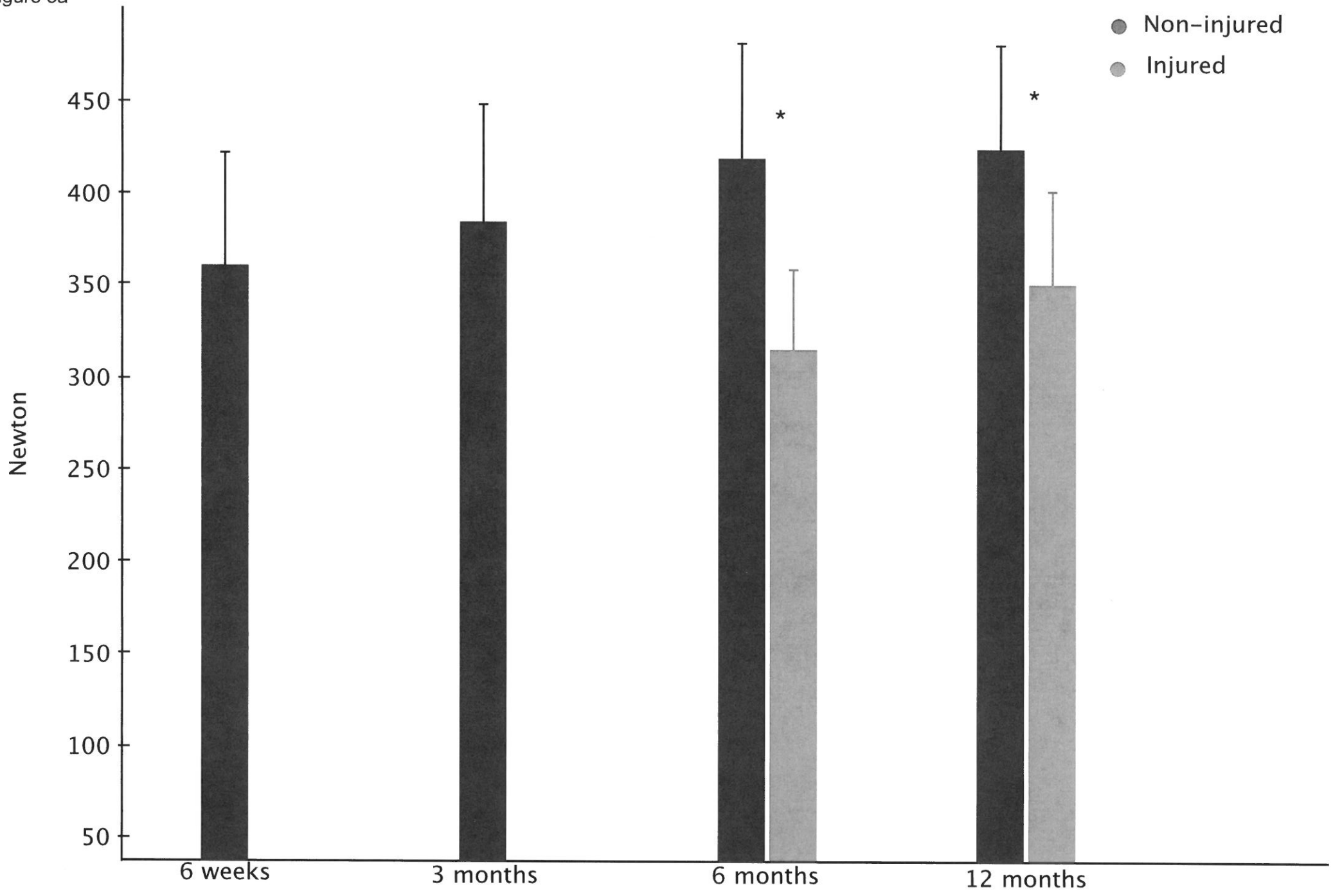
Non-injured
Injured
Newton
450
400
350
300
250
200
150
100
50
*
*
6 weeks
3 months
6 months
12 months

Figure 3c

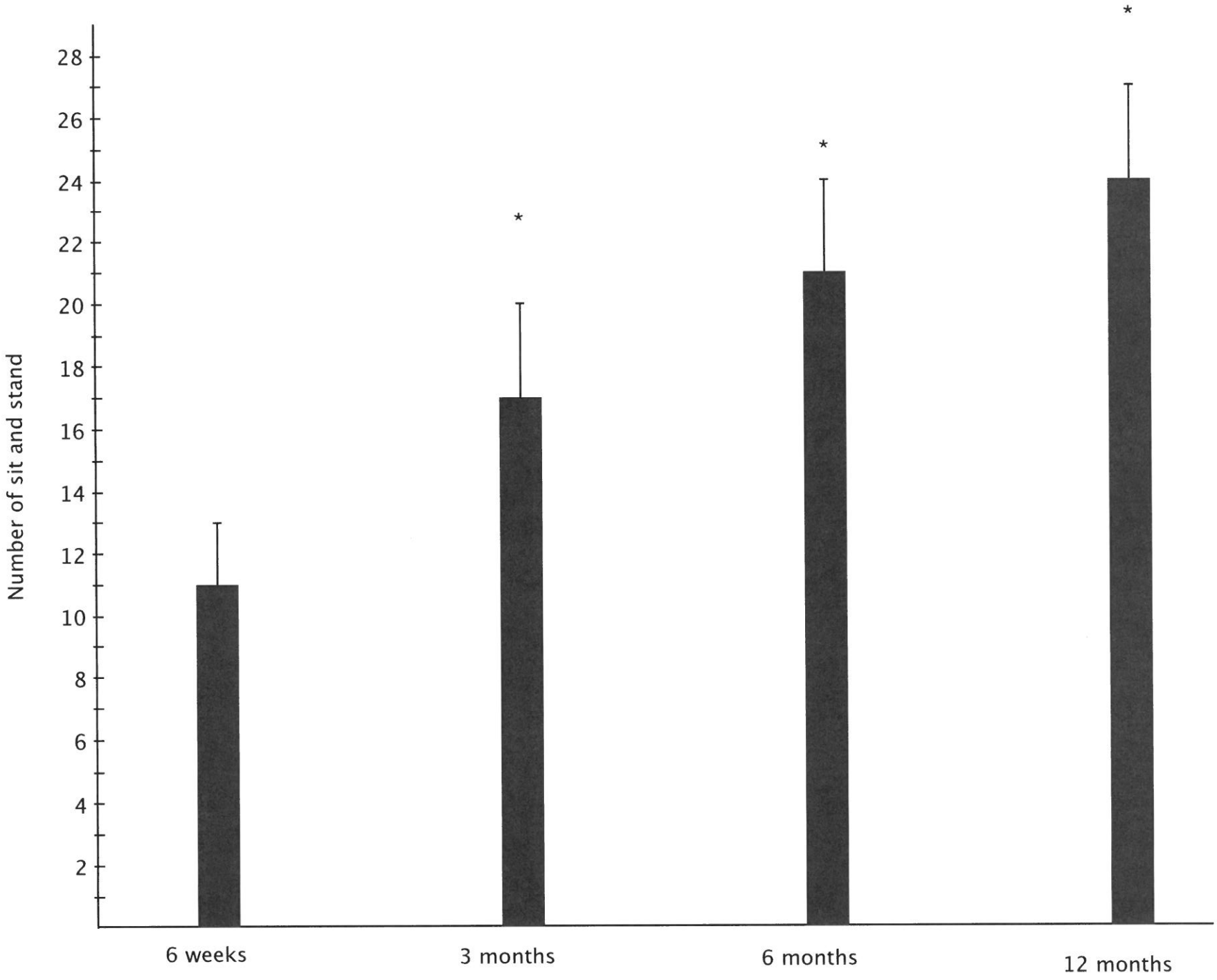
Number of sit and stand
28
26
24
22
20
18
16
14
12
10
8
6
4
2
*
*
*
6 weeks
3 months
6 months
12 months

Table 1: Baseline characteristics of the 49 patients

Age at time of fracture, mean (range)	43.1(18-79)
Gender, male/female	32/17
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	12/37
Fracture classification AO-42-	
A	30
B	14
C	5
Open/closed fracture	6/43
Fibula fracture, no/yes	5/44
Aditional tratment besides intramedullary nailing	
Initiel screw fixation of posterior aspect of the distal tibia	14
Matatarsfracture treated with Kirschner-wire	2
Complications	
Compartment syndrom	1
Broken screws	2

Table

Tabel 2: KOOS outcomes 12 months after intramedullary nailing of an tibial shaft fracture

		KOOS				
		PAIN	ADL	SYMP	QOL	SPORT
Study population	Mean	84.5	86.4	86.9	63.4	57.2
	95% CI	79.5 – 89.5	81.5 – 91.3	82.7 – 91.1	55.5 – 71.3*	47.6 – 66.8*
Reference population **,***	95% CI	86.7 – 88.2	86.5 – 88.1	85.4 – 86.9	77.4 – 79.6	72.5 – 75.1