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Influence of flexible nailing in the later phase of fracture healing: strength and mineralization in rat femora

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Abstract In this experimental study, the influence of flexible nailing in the later phase of femoral fracture healing was investigated. Sixty rats were randomly assigned to three groups. In 20 rats no intervention was performed, and they served as a control group. Fracture and reamed nailing with a rigid steel nail was performed in the left femur in the other 40 rats. These rats were reoperated after 30 days, and the medullary nail was removed. In one group (20 rats) a flexible polyethylene nail was installed (flexibly nailed group), while the rats in the other group received a steel nail identical to the one that was removed (rigidly nailed group). At 60 and 90 days, the left femurs of 10 animals in each group were studied clinically, radiologically, and biomechanically, and bone mineralization was measured by dual-energy X-ray absorptiometry. Radiographs in two planes revealed a clearly visible fracture line in both intervention groups at 60 days. At 90 days, the fracture line was clearly visible in the flexibly nailed group, while bridging callus was apparent after the rigid nailing. At 60 and 90 days, the callus area in the flexibly nailed group was significantly larger than that in the rigidly nailed bones. Biomechanically, flexible nailing reduced maximum bending load and fracture energy at 60 and 90 days compared with findings in rigidly nailed bones, while bending rigidity was similar in the two groups. All values for biomechanical characteristics were reduced at 60 and 90 days in flexibly nailed bones compared with intact femurs, while in the rigid nailing group, bending load and fracture energy were similar to those in intact bones at 90 days. Bone mineral content in the callus segment and diaphysis was greater in the rigidly nailed bones than in the flexible nailing group at 60 days, while at 90 days, no differences were detected. In conclusion, this animal study indicates that: (1) flexible nailing in the later phase of fracture healing increases callus formation, while (2) the quality of bone healing is reduced.

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Key words Bone healing · Bone mineralization · Flexible nailing · Mechanical strength

Introduction

Major factors that determine the mechanical milieu of a healing bone are the fracture configuration, the accuracy of fracture reduction, the rigidity of the fixation device, and the amount and type of stress at the fracture gap, dictated by functional activity and loading. At least four different fundamental modes of loading can be envisioned in a healing transverse fracture, each producing a different type of relative motion at the fracture site.[31] Tensile loading produces distraction at the fracture site, while compressive loading produces impaction. Torsion produces shearing, while bending results in compression (impaction) at one surface, combined with tension (distraction) at the opposing surface. The consequences of differents type and degrees of motion between the bone ends have been studied under plate fixation,[8,18,22,24,26] external fixation,[2,9,11,21] and medullary nailing.[20,29,31] Studies of medullary nailed fractures indicate a negative effect of torsional instability.[19] Flexible nailing stimulates callus formation,[3,30] while, with this method, alignment and fracture apposition is questionable. The effects on healing of increased compression at the fracture site, brought about by removing interlocking screws, i.e., dynamization, have been addressed in clinical and experimental studies.[4,10,14,28,32] Dynamization, however, causes a general increased instability at the fracture site, while the influence of increased instability in the later phase of bone healing, produced by callus formation, has been less extensively studied. Our objective, then, was to evaluate the effects of flexible nailing in the later phase of healing, focusing on the regaining of mechanical strength and bone mineralization in a femoral fracture model in rat.

Materials and methods

Experimental animals

Sixty 16-week-old male Wistar rats (Møllegård Avlslaboratorium, Eiby, Denmark), weighing 331–389g, were used. The animals were housed in cages (with two animals in each), and received a standard rodent diet (R.M. 1; Special Diet Services, N. Humberside, UK), with a calcium content of 0.71% and a phosphorus content of 0.5%, and tap water provided ad libitum. The light cycle was 12h or 12h off. The experiment conformed to the Norwegian Council Animal Research Code for the Care and Use of Animals for Experimental Purposes.

Treatment regimen

The rats were randomly assigned to a control group and two intervention groups; each containing 20 animals. The control group (in which no intervention was performed) supplied dimensional, mechanical, and mineralization data of intact femurs at 60 and 90 days. In the 40 intervention animals, a standardized surgical procedure was performed. After intraperitoneal anesthesia was produced (pentobarbital, 5mg/100g body weight; Temgesic [Schering-Plough, Kenilworth, NJ, USA]; 0.3ml), the left femur was exposed between the lateral vastus and hamstrings. The muscles were carefully elevated in the lateral part, and a partial osteotomy engaging, one-third of the diaphysis, was made with a fine-toothed circular saw blade mounted on an electrical drill. The osteotomy was made at the end of the trochanteric ridge approximately 13mm from the top of the greater trochanter, and the femur was then broken manually. The medullary canal was successively reamed from the osteotomy site in a proximal direction through the top of the greater trochanter and in a distal direction to the level of the condyles, to a diameter of 1.6mm, using steel burrs mounted on the electrical drill. This procedure secured a central position of the reamer in the medullary cavity. The fracture was reduced manually, and a steel nail was inserted from the trochanter to the femoral condyles for stabilization (Fig. 1).

Thirty days after the fracture and nailing, all rats in the intervention groups were reoperated, and exchange nailing was performed. In one group (20 rats) the stainless steel nail was removed, and a flexible polyethelene nail was inserted. In the other 20 animals, the steel nail was removed, and an identical nail was reintroduced. The stainless steel nail had a bending rigidity of 483.22N/mm (range, 458.46–505.85N/mm) (median and interquartile range of five tested nails), while the polyethylene nail had a bending rigidity of 80.36N/mm

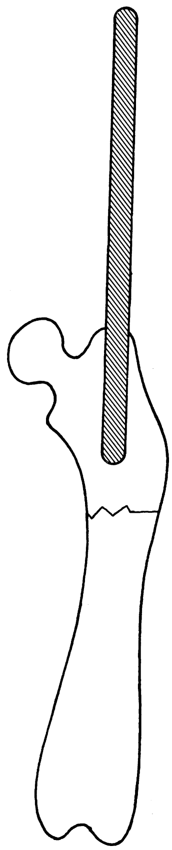
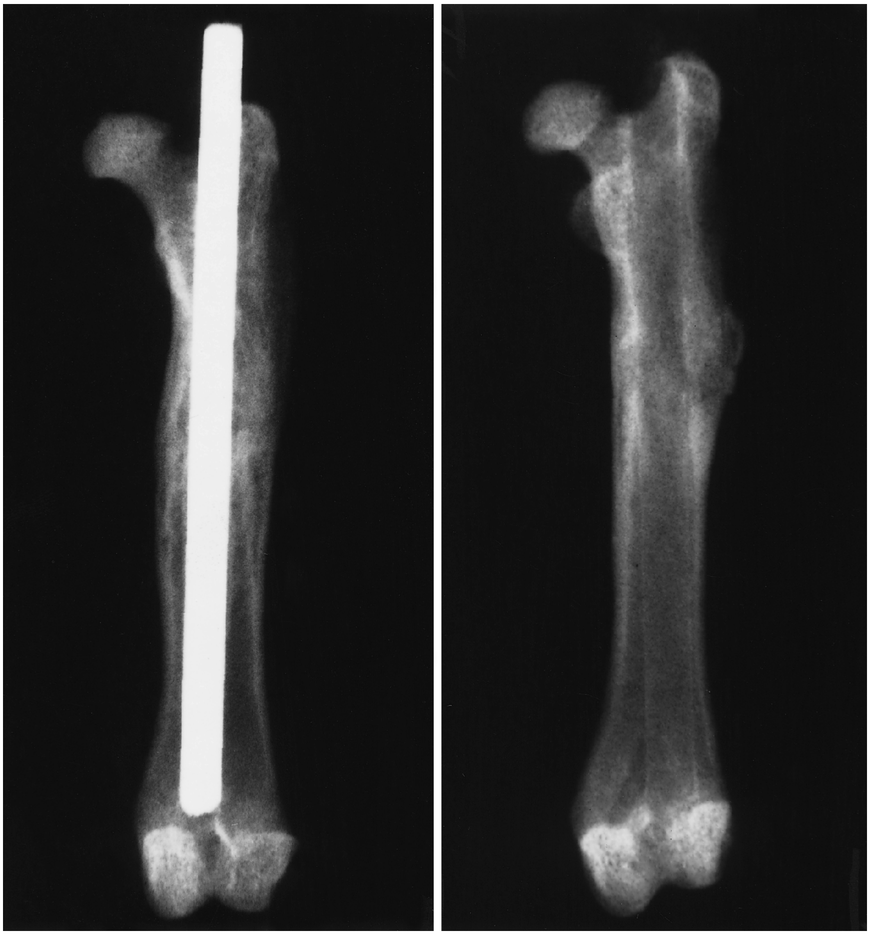


Fig. 1. Fracture model of rat femoral bone with antegrade nailing

(range, 76.11–86.24N/mm). For comparison, the bending rigidity of intact femurs at the start of the experiment was 392.00N/mm (range, 354.22–420.56N/mm); at 60 days, it was 475.48N/mm (range, 428.96–519.31N/mm), and at 90 days it was 534.83N/mm (range, 409.82–442.10N/mm). Mechanical data for the materials showed that the ultimate shear strength for the steel and polyethylene nails was 221 MN/m^2 and 34 MN/m^2, respectively. For comparison, values for cortical bone are 46–87 MN/m^2. All nails were cylindrical, with a diameter of 1.6mm and a length of 36mm, and were rubbed with 1000-grit silicone paper to produce a uniform surface roughness. Fixation was achieved without radiographic control. Proper nail placement was confirmed by radiographs taken at the end of the experiment (Fig. 2). The wounds were closed in two layers.

Specimens

At 60 and 90 days post-fracture (30 and 60 days after exchange nailing) 10 rats in each group were killed in a carbon dioxide chamber, and the left femurs were dissected free from soft tissue. Anteroposterior and transverse diameters of the callus region were measured with a sliding caliper (accuracy of 0.01mm). The quantity of



a b

Fig. 2a,b. Radiographs (**a** steel and **b** polyethylene nails in situ) of left femoral bones 90 days after exchange nailing

callus was expressed as the gross cross-sectional area, assuming it to be elliptical. The anteroposterior and transverse diameters of the distal diaphyseal area 10mm proximal to the medial condyle were also measured, assuming the cross-section to be elliptical. The bones were subsequently radiographically examined in two planes and the intramedullary devices removed. The bones were stored in sealed test tubes at −80°C.

The femurs were examined by dual energy X-ray absorptiometry (DEXA). DEXA was performed on a Lunar DPX (Lunar Corporation, Madison, WI, USA) equipped with a 4.75-mA X-ray generator and a Small Animal software program. The collimated value (size of the X-ray beam at the source) was 0.84mm, and the sample interval was 1/64s. The high resolution scan mode had a sample size of 0.15 × 0.3mm, and a series of transverse scans from the top of the trochanter to the tip of the condyles (scan area of 30 by 40mm) lasted 7min for the total femur determination, receiving 1.92mrem of radiation. Each femur was placed on a 2-cm-long piece of lucite during scanning. After the scanning procedure, a 3-mm region of interest (ROI) was measured between 12 and 15mm from the top of the greater trochanter, corresponding to the callus region. A 3-mm segment of the distal diaphysis 10mm proximal to the medial condyle was also measured.

One femur in the control group (90 days) was scanned ten times for the determination of the reproducibility of the method. The coefficient of variation for the mean value of ten DEXA measurements for bone mineral content (BMC) was 3.7%, 3.9% and 1.9% in the proximal, distal, and total femur, and for bone mineral density (BMD) it was 2.3%, 2.1%, and 1.1%, respectively.

The specimens were placed in a moisture chamber at room temperature prior to the mechanical testing. A three-point bending test was performed, with bending applied in the plane of natural extension. The bones were placed in a jig with two horizontal bars with a diameter of 3mm, mounted on roller bearings. The distance between the bar axies was 13mm. The midpoint was a blunt metal edge moved by the crosshead of a mechanical testing machine (model 852.02, Mini Bionix Test System; MTS Systems, Eden Prairie, MN, USA). The femur was placed with the lesser trochanter proximal to, and in contact with the proximal transverse bar of the jig. This arrangement placed the point of force application over the fracture site at the end of the trochanteric ridge, which corresponds to the narrowest part of the medullary cavity. However, when the femur had angular or rotational deformities, approximation of this arrangement was made as the bone was placed in a stable position to avoid slippage during testing. Bending was applied successively, determined by the degree of strain (ductility) of the femur, calculated with the Test Star software program. Observations of stress and strain were recorded for strain values in 0.05-mm increments, and stress/strain curves were made. Bone strength, structural stiffness (rigidity), and fracture energy were determined. The maximum bending load at failure (newtons) was interpreted as the strength of the bones. The structural stiffness or rigidity (newtons per mm deflection) was calculated as the linear slope of the curve between 20% and 70% of maximum load value. Fracture energy was calculated as the area under the curve to the fracture point.

Statistics

The results are presented as median values with upper and lower quartiles. Each variable in the three experimental groups was tested at 60 and 90 days by analysis of variance (Kruskall-Wallis test). When significance was confirmed, each variable was tested between groups at the two experimental times by the Mann-Whitney *U*-test, which was also applied for testing differences in each variable within groups between 6 and 12 weeks. The level of significance was set at $P < 0.05$.

Results

The animals in the intervention groups tolerated the initial operation well and resumed walking on the first postoperative day and full weight-bearing after 1–2 weeks. Reoperation after 30 days produced no adverse effects on the functional status of the involved limb. One rat in the flexibly nailed group (90 days) was excluded because of proximal migration of the nail.

The fractures in the intervention groups healed with the production of external callus, and radiographs revealed a radiolucent fracture line at 60 days in both groups. At 90 days, a bridging callus was seen in the rigidly nailed bones, while the fracture line still was clearly visible after flexible nailing.

Table 1. Cross-sectional area of callus/proximal diaphyseal region and diaphysis (mm^2) in control group and in flexibly and rigidly nailed groups at 60 and 90 days after fracture

	Control	Flexible nailing	Rigid nailing
Callus/proximal diaphysis			
60 Days	15.00 (13.56–15.97)	46.39 (39.74–54.62)	32.95 (29.10–43.57)
P Control vs Flexible	0.001		
P Flexible vs Rigid		0.049	
P Control vs Rigid	0.001		
90 Days	15.41 (13.88–16.32)	42.71 (35.33–53.57)	29.85 (26.86–40.22)
P Control vs Flexible	0.001		
P Flexible vs Rigid		0.034	
P Control vs Rigid	0.001		
Diaphysis			
60 Days	13.00 (11.80–13.66)	19.43 (15.77–23.21)	18.57 (15.50–26.50)
P Control vs Flexible	0.001		
P Flexible vs Rigid		0.88	
P Control vs Rigid	0.001		
90 Days	13.81 (13.31–14.56)	17.80 (16.56–20.97)	17.25 (16.64–19.17)
P Control vs Flexible	0.001		
P Flexible vs Rigid		0.65	
P Control vs Rigid	0.001		

Values in boxes are *P* values between groups
Median and 25th and 75th percentiles are given

Table 2. Bending load (N), bending rigidity (N/mm), and fracture energy (Nmm) in control group and in flexibly and rigidly nailed groups at 60 and 90 days after fracture

	Control	Flexible nailing	Rigid nailing	P Control vs Flexible	P Flexible vs Rigid	P Control vs Rigid
Bending load						
60 Days	253.19 (209.33–257.82)	90.64 (62.78–164.67)	197.74 (173.91–208.28)	0.001	0.01	0.016
90 Days	272.88 (222.54–278.09)	136.07 (91.57–194.89)	252.14 (231.50–297.02)	0.001	0.01	0.82
Bending rigidity						
60 Days	475.48 (428.96–519.31)	152.56 (51.50–384.37)	285.37 (248.03–469.71)	0.01	0.08	0.02
90 Days	534.83 (521.81–567.25)	199.13 (122.83–405.24)	366.35 (312.46–545.02)	0.001	0.08	0.02
Fracture energy						
60 Days	91.15 (83.91–100.73)	40.47 (32.74–47.32)	67.15 (46.70–81.86)	0.002	0.01	0.001
90 Days	97.52 (74.24–113.56)	60.29 (50.08–63.96)	94.06 (70.87–102.36)	0.02	0.01	0.65

Values in boxes are P values between groups
Median and 25th and 75th percentiles are given

At 60 and 90 days, the callus area was significantly increased after flexible nailing compared with that after rigid nailing (Table 1). Between 60 and 90 days, bending load and fracture energy increased in the rigidly nailed bones ($P = 0.02$) (Table 2), while the increase was not significant after flexible nailing ($P = 0.17$ and $P = 0.06$). Bending rigidity did not increase significantly. After flexible nailing, bending load and fracture energy were significantly lower at 60 and 90 days than after rigid nailing. At 90 days, rigidly nailed bones had acquired a bending load and fracture energy similar to that of intact bone, while the bending rigidity was still lower than that of intact bones.

At 60 days, rigidly nailed bones had increased bone mineral content in the callus segment and diaphysis compared with findings in the flexible nailing group. However, bone mineral density and bone mineral content increased significantly between 60 and 90 days in the flexibly nailed bones, both in the callus segment and diaphysis, and in the total femur ($P < 0.05$) (Tables 3

Table 3. Bone mineral content (g) of callus/proximal diaphyseal region, diaphysis, and total femur in control group and in flexibly and rigidly nailed groups at 60 and 90 days after fracture

	Control	Flexible nailing	Rigid nailing	P (Control vs Flexible)	P (Flexible vs Rigid)	P (Control vs Rigid)
Callus/proximal diaphysis						
60 Days	0.044 (0.039–0.046)	0.052 (0.048–0.055)	0.059 (0.053–0.073)	0.002	0.02	0.001
90 Days	0.048 (0.043–0.049)	0.071 (0.058–0.090)	0.064 (0.060–0.070)	0.001	0.38	0.001
Diaphysis						
60 Days	0.033 (0.031–0.035)	0.038 (0.035–0.042)	0.041 (0.037–0.045)	0.04	0.01	0.21
90 Days	0.033 (0.032–0.035)	0.038 (0.035–0.042)	0.041 (0.037–0.045)	0.004	0.57	0.01
Total femur						
60 Days	0.546 (0.475–0.579)	0.572 (0.496–0.617)	0.624 (0.573–0.697)	0.36	0.12	0.01
90 Days	0.605 (0.543–0.640)	0.731 (0.660–0.809)	0.649 (0.612–0.757)	0.01	0.29	0.06

Values in boxes are *P* values between groups
Median and 25th and 75th percentiles are given

and 4, respectively), while, after rigid nailing, no significant increases in BMC or BMD were observed in these regions. At 90 days, there were no significant differences in BMC and BMD between the two intervention groups.

Discussion

Interfragmentary motion influences callus formation and the healing of fractures. The optimal biomechanical conditions for bone healing, however, remains unclear. Instability such as bending and compression initiates bone formation on the periosteal surface.[16,21,25] This has been attributed to local strain in the bone. Also, loading disrupts or compresses blood vessels, leading to local tissue ischemia,[21] and transient ischemia may initiate osteogenic differentiation of the periosteal cells.[23] On the other hand, rotational and shear movements have been shown to have detrimental effects on fracture healing.[19] Previous experimental studies have indicated favorable effects of moderately flexible intramedullary fixation, and also of controlled axial and shear micromotion on bone healing.[3,29,30] Furthermore, it has

Table 4. Bone mineral density (g/cm^2) of callus/proximal diaphyseal region, diaphysis, and total femur in control group and in flexibly and rigidly nailed groups at 60 and 90 days after fracture

	Control	Flexible nailing	Rigid nailing
Callus/proximal diaphysis			
60 Days	0.295 (0.268–0.314)	0.305 (0.287–0.336)	0.306 (0.281–0.357)
90 Days (boxes: Control–Rigid 0.08; Control–Flexible 0.01; Flexible–Rigid 0.17)	0.322 (0.303–0.343)	0.366 (0.338–0.433)	0.356 (0.305–0.369)
Diaphysis			
60 Days (boxes: Control–Rigid 0.59; Control–Flexible 0.003; Flexible–Rigid 0.09)	0.216 (0.205–0.220)	0.189 (0.170–0.208)	0.206 (0.192–0.241)
90 Days	0.213 (0.199–0.237)	0.221 (0.208–0.232)	0.252 (0.217–0.276)
Total femur			
60 Days	0.264 (0.247–0.277)	0.268 (0.248–0.284)	0.288 (0.269–0.317)
90 Days	0.279 (0.263–0.294)	0.309 (0.273–0.320)	0.299 (0.274–0.317)

Values in boxes are *P* values between groups
Median and 25th and 75th percentiles are given

been indicated that flexible nails prevent stress protection, without a delay in union.[20]

In the present study in rats, we found that flexible nailing in the later phase of bone healing by producing callus, reduced the values for the mechanical characteristics as evaluated at 60 and 90 days after fracture. This was associated with reduced mineralization at 60 days.

The healing of diaphyseal femoral fractures in rats takes about 12 to 16 weeks before mechanical properties equivalent to those of intact bone are restored.[6,20] At 30 days, when a diffuse periosteal callus is present, we removed the rigid nail and installed either a new rigid nail or a flexible nail with a rigidity between 18% and 20% of that of the intact femur. Although flexible, this nail provided an implant/bone construct capable of maintaining fragment apposition, while permitting increased interfragmentary motion; as indicated by the production of periosteal callus.

The animals were 16 weeks old at the time of fracture and nailing. At this time they were sexually and skeletally mature.[7] However, complete closure of the femoral epiphysis in rats occurs late in life, i.e., between 18 and 24 months of age.[15] The values for mechanical characteristics, as well as those for mineralization in the rat femoral bone, then, tend to increase up to this time.[19,27]

Animal research in bone healing indicates that strength is gained at a higher rate during the first phases of healing with rigid fixation as compared with flexible.[28] It is suggested that the growth of callus progressively restricts interfragmentary motion at the fracture site until its structure is of sufficient size and stiffness to reduce strain sufficiently to allow the subsequent processes of bone remodelling to commence. The present study was designed to secure a stable nailing during the first phase of healing and to investigate the effects of increased flexibility in the later phase. We found that instability induced an increased callus area that was immature with reduced mechanical properties. This indicates that, when bone union is achieved, the presence of a nail that is less rigid that the bone itself may interfere with effective remodelling at the fracture site.

Our observations could, in some way, be relevant to the dynamization of nailed fractures in clinical practice. Dynamization, by the removal of screws from one or both sides of the fracture site, has been recommended by several authors to promote healing.[4,10,14] However, dynamization has not gained general acceptance in routine trauma care. Fragment apposition and alignment of the bone have been questioned, and so far the effects of dynamization have not been adequately documented, as no controlled studies have been done. In our experiement, we chose a rigid nailing situation for the first 30 days, followed by flexible nailing. No monitoring of the degree of interfragmentary motion was performed, but radiographs taken at 60 and 90 days revealed no dislocation or malalignment at the fracture gap, as indicated in Fig. 2. Our experiments indicate that dynamization which provokes instability in the later phase of bone healing may influence remodelling at the fracture site in a negative way.

One of the early responses of bone to trauma is an increase in the rate of mineral turnover. Many investigators have reported a significant reduction in bone mineral mass after the fracture of long bones in humans, not only at the fracture site, but also at adjacent sites both proximal and distal to the fracture.[5] This persists after union, but there is a wide range in both the amount of loss and the extent of recovery. We did not observe reduced mineral mass of the femoral bone as fracture healing proceeded. Reported differences may be caused, in part, by the variable accuracy of the techniques used in the measurement of bone mass.[1,17]

Investigations of such fixation devices as plating have documented weakening of bone through the loss of bone mass and structure under the plate. It has long been thought that this negative effect may be a consequence of two processes; the interference of plates with the cortical blood supply, which causes necrosis, followed by porosis and stress shielding of bone, followed in turn, by structural changes according to Wolff's law. The extent to which either of these two processes influence the weakening of bone remains a matter of debate.[1] Studies of medullary nailed intact femora indicate that rigid nails produce a higher degree of stress protection, evaluated by in-vivo strain measurements and porosity, than less rigid nails.[12,13] However, after flexible nailing we observed a tendency toward reduction of mineralization at 60 days, as compared with findings after rigid nailing. This may have been caused by a general influence on mineralization brought about by increased interfragmentary strain; however, mineralization tended to normalize between 60 and 90 days.

In conclusion, this experiemental study indicates that flexible nailing in the later phase of fracture healing, by callus production, has a detrimental effect as compared with that of intramedullary nails with a rigidity close to that of intact diaphyseal bone.

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