

Effect of Low Molecular Weight Heparin on Fracture Healing in a Stabilized Rat Femur Fracture Model

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The purpose of this study was to evaluate the effect of low molecular weight heparin (LMWH) on fracture healing in a standard stabilized rat femur fracture model. A closed, mid-diaphyseal transverse fracture was created in the right femur of Long-Evans rats after insertion of a 0.8-mm K-wire into the medullary canal. Animals were randomized to receive either LMWH (70 units/kg dalteparin) or an injection of normal saline daily for 2 weeks. Animals were sacrificed at 2, 3, and 6 weeks. Fracture healing was assessed by radiographs, histology, and mechanical testing. There were no significant differences between the control and LMWH groups in the percentage of animals with radiographic bridging callus at each time point. Histologic appearance of fracture healing was similar between the control and LMWH groups. There were no significant differences in the normalized mechanical properties of the control and LMWH groups at 2 and 3 weeks. At 6 weeks, the percent torque of the LMWH group was significantly greater than the control group ($p = 0.0072$), however, there was no significant difference in the stiffness and energy absorption. Dalteparin, at the dosage used in this study, did not impair fracture healing in this standard stabilized rat femur fracture model.

INTRODUCTION

Despite common usage, little is known about the effect of low molecular weight heparin (LMWH) on fracture healing. Street and colleagues have reported a significant delay in fracture healing following the administration of LMWH in an unstabilized rabbit rib fracture model.¹ Both standard heparin and LMWH have been shown to have deleterious effects on bone, causing osteoporosis, stimulating bone resorption, increasing calcium loss, and decreasing bone turnover.²⁻⁹ Concern has also been raised that the impairment of bone formation by heparin may adversely affect integration of porous ingrowth prostheses.¹⁰

Thromboembolic complications are the most common preventable cause of mortality and morbidity in the trauma patient.¹¹⁻¹⁷ For this reason, the vast majority of trauma patients with orthopedic injuries receive some form of thromboembolism prophylaxis, either by mechanical or pharmacological means, or both. Decisions regarding

thromboembolism prophylaxis often requires physicians to weigh complex risks and benefits of different treatment options. A recent meta-analysis compared the efficacy of heparin, warfarin, and LMWH and found LMWH to be superior in preventing thromboembolism.¹⁸ LMWH is easily administered and requires little or no laboratory monitoring.¹⁹ Therefore, LMWH has become a popular method of thromboembolism prophylaxis in the trauma patient. Because large numbers of trauma patients with lower extremity and pelvic fractures routinely receive LMWH prophylactically, it is imperative to consider whether LMWH may have an adverse impact on fracture healing.

METHODS

Male Long-Evans rats, with a mean age of 13 weeks (range, 12–15 weeks) and a mean bodyweight of 391 g (range, 346–434 g), were used. The study protocol was approved by the local Institutional Animal Care and Use Committee, and all animal experimentation was carried out with adherence to NIH and the Committee guidelines. All surgical procedures were performed under sterile operating conditions with the rats under general anesthesia (4% halothane inhalation followed by intra-peritoneal injection of 80 mg/kg ketamine hydrochloride and 8 mg/kg xylazine hydrochloride). A 1-cm lateral parapatellar incision was made and the patella displaced laterally to expose the distal femoral condyle of the right hind limb. A 0.8-mm diameter K-wire (Synthes, Paoli, PA) was inserted into the femoral canal in a retrograde fashion starting from the trochlear groove and advancing proximally through the greater trochanter until the distal end was flush with the femoral condyle. A small incision was then made over the greater trochanter and the K-wire was cut flush with the proximal end of the femur. The wounds were then irrigated and closed using 4.0 nylon suture. A closed, transverse, mid-shaft fracture was then created in the pinned femur using a three-point bending apparatus with a drop weight as described by Bonnarens and Einhorn.²⁰

Radiographs were taken immediately postoperatively to verify proper intramedullary wire placement and fracture configuration. Any rats with comminuted fractures were excluded from the study. Animals were permitted full weight bearing and unrestricted movement upon awakening from anesthesia. Postoperative pain was controlled using a peritoneal injection of 0.05 mg/kg buprenorphine hydrochloride initially and oral buprenorphine suspended in gelatin twice daily for 2 days.

The animals were randomized to either the LMWH group, receiving 70 units/kg dalteparin sodium (Fragmin, Pfizer, New York, NY), or to the control group, receiving the same volume of normal saline. The subcutaneous injections were administered once daily to alternate sites of the anterior abdominal wall for 14 days beginning on postoperative day 1. Animals were maintained for intervals of 2, 3, and 6 weeks. Euthanization was carried out with inhalation of carbon dioxide gas.

Radiologic Evaluation

Standardized radiographs (Faxitron, Wheeling, IL) were performed using constant settings with the animal anesthetized and positioned prone with both hind limbs fully abducted. They were obtained immediately post-operatively to confirm satisfactory fracture configuration and proper K-wire position. Similar radiographs were taken at the time of sacrifice, and fracture union was evaluated by two, blinded, independent observers. Fracture union was defined as the presence of bridging callus along opposite cortices. In five cases when the reviewers differed in their interpretation, the classification of healed versus not healed was made by consensus agreement.

Histological Evaluation

Four animals from each group and time point were randomly selected for histological analysis. The fractured femur was harvested and fixed in 4% paraformaldehyde in 0.1 M phosphate buffer for 24 h at 4°C, and then defatted in methanol, decalcified with 10% formic acid in citrate for 4 days, and embedded in paraffin. All specimens had adequate soft callus to maintain the position of the proximal and distal fragments. Specimens were sectioned longitudinally in 4- μ m sections and stained with hematoxylin and eosin. The degree of fracture healing was evaluated using a five-point qualitative scale proposed by Allen et al.²¹ According to this classification system, grade 4 represents complete bony union, grade 3 represents an incomplete bony union (presence of a small amount of cartilage in the callus), grade 2 represents a complete cartilaginous union (well-formed plate of hyaline cartilage uniting the fragments), grade 1 represents an incomplete cartilaginous union (retention of fibrous elements in the cartilaginous plate), and grade 0 indicates the formation of a pseudoarthrosis (most severe form of arrest in fracture repair).

Mechanical Evaluation

The remaining specimens were subjected to mechanical testing. Following euthanasia, both the fractured femur and the intact femur on the contralateral side were dissected free of surrounding soft tissue and the intramedullary K-wire was removed. Sufficient soft callus was present in all specimens to maintain the relationship between the proximal and distal fragments. The specimens were centered in two colinearly positioned cylindrical pots and imbedded in Wood's metal (Alfa Aesar, Ward Hill, MA). The distal end of the femur was first positioned by centering the long axis of the bone and securing it with Wood's metal. A custom jig was then used to position the proximal end of the femur for imbedding in the second cylindrical pot. The specimens were then mounted in a Frankel-Burstein axial torsion machine modified to operate under computer control.²² The standard swinging-pendulum mechanism was replaced with a

stepper motor (model 083062-1-8- 031-010, Parker Compumotor, Rohnert Park, CA). Rotational displacement was measured with a precision potentiometer (model 793341-14092, Gould Instrument Division, Cleveland, OH), and torque was measured with a 0.7 Nm torque cell (model 2105, Eaton Corporation, Troy, MI). Specimens were tested in torsion at a rate of 50 degrees per minute through an arc of 45 degrees. Rotational displacement and torque data were collected at 60 Hertz using a digital data acquisition system (model K500A, Keithley Instruments, Cleveland, OH). Maximum torque to failure was measured directly from the data, and the torsional stiffness was calculated from the regression of the linear portion of the torque versus the angular displacement curve. The energy absorption to maximum torque was calculated as the area under the curve to the maximum value. All biomechanical measurements were repeated on the intact, contralateral femur in an identical manner. For each animal, the stiffness, maximum torque to failure, and energy absorption to maximum torque were each calculated as a percentage of the intact femur to allow for accurate comparison between animals.

Statistical Analysis

A two-factor analysis of variance (ANOVA) was performed on the normalized data of the biomechanical properties to account for individual animal differences. The factors were the time point (2, 3, and 6 weeks) and the experimental group (control or LMWH). Significance was defined as *p* values less than 0.05. When appropriate, a Bonferroni-Dunn post hoc test was performed to determine differences between the factors at each time point.

RESULTS

Nine animals were excluded from the study. One animal died of unknown causes on postoperative day 1, and four others died of anesthetic complications while undergoing radiographs. Four other animals were excluded because the the initial postoperative radiograph showed fracture comminution. No clinical evidence of infection was noted in any animals during this study.

Radiologic Evaluation

A varying degree of callus was seen at 2 weeks, but none of the fractures showed clear evidence of bridging callus in either the control (Fig. 1A) or LMWH group (Fig. 1D). At 3 weeks, one-third (4/12) of the control group (Fig. 1B) and one-third (4/12) of the LMWH group (Fig. 1E) showed clear evidence of bridging callus on opposite cortices. At 6 weeks, 62% (8/13) of control group (Fig. 1C) and 67% (8/12) of LMWH group (Fig. 1F) showed clear evidence of bridging callus on opposite cortices.

Histological Evaluation

Two weeks following fracture, both control (Fig. 2A) and LMWH (Fig. 2D) specimens had abundant callus formation. Newly formed woven bone (intramembranous ossification) surrounded the fracture peripherally, while abundant nonbridging chondrocytes were present centrally. At 3 weeks, there was increased evidence of endochondral ossification in both the control (Fig. 2B) and LMWH (Fig. 2E) specimens. Chondrocyte areas were smaller, and some specimens showed evidence of partial bone bridging. At 6 weeks, there was further evidence of fracture healing in both the control (Fig. 2C) and LMWH (Fig. 2F) specimens, with complete replacement of chondrocytes by bridging bone in most specimens.

Histological grading of the fracture healing was similar between the control and LMWH groups. At 2 weeks, all specimens in both groups were graded 2. At 3 weeks, the fracture healing grade ranged from 2 to 3, with the mean being 2.5 in both groups. At 6 weeks, the fracture healing grade ranged from 3 to 4, with a control group mean of 3.5 and LMWH group mean of 3.75.

Mechanical Testing

The means and standard deviations of the maximum torque to failure, stiffness, and energy absorption to maximum torque are shown in Table 1. The maximum torque and stiffness of the control group fractured femurs increased between each time point, with the mean maximum torque and the mean stiffness approaching that of the intact femurs at 6 weeks. In the LMWH group, there was a less dramatic increase between 2 and 3 weeks, but by 6 weeks the mean maximum torque and mean stiffness also approached that of the intact femurs. A post hoc power analysis of the mechanical data was performed. The power for the maximum torque and stiffness was >0.9, while the power for energy was 0.42.

To account for variation in animal size, the maximum torque, stiffness, and energy absorption values were normalized by the respective values of the contralateral intact femurs. The mean and standard deviations of the percent maximum torque, percent stiffness, and percent energy were calculated for each group (Fig. 3). There were no significant differences in the normalized mechanical properties of the control and LMWH groups at 2 and 3 weeks. At 6 weeks, the percent torque of the LMWH group (0.864 ± 0.288) was significantly greater ($p=0.0072$) than the control group (0.609 ± 0.165), however, there was no significant difference in the stiffness and energy absorption.

DISCUSSION

Street et al. reported a significant delay in fracture healing following the administration of enoxaparin in an unstabilized rabbit rib fracture model.¹ Fracture healing was assessed by histology, histo-morphometry, and immunohistochemistry at days 3, 7, and 14, and by mechanical testing at 21 days following fracture. At days 3, 7, and 14, they found fewer proliferating cells and fewer transforming pericytes in the medullary callus of the enoxaparin-treated rabbits. In the enoxaparin group, the histologic grade of fracture healing was reduced at days 7 and 14, and the mechanical properties were weaker at day 21 compared to the control animals. Because of Street and coworkers' finding that low molecular weight heparin impaired fracture healing, we investigated the use of dalteparin in a standard stabilized rat femur fracture model. In contrast to the findings of Street et al., in the current study we found that administration of LMWH did not have any deleterious effect on fracture healing mechanical properties.

Other previous reports have also described deleterious effects of anticoagulants, in particular heparin, on bone repair. In 1956, Stinchfield et al. demonstrated that daily administration of standard heparin or warfarin significantly impaired fracture repair in rabbit and canine models.⁹ Several studies have also identified the long-term use of heparin as a risk factor for the development of osteoporosis in humans.^{2,4,5,7,8} Chowdhury et al. concluded that low doses of standard heparin directly stimulated bone resorption by increasing the number of differentiated osteoclasts and by enhancing the activity of individual osteoclasts.³

Several studies have suggested that LMWH may have less deleterious effects on bone homeostasis. In fetal rat calvaria culture, LMWH produced significantly less calcium loss than heparin.²³ Matzsch et al. demonstrated that LMWH stimulated bone resorption to a lesser degree than did heparin, although overall density decreased to a similar extent with both agents.⁷ In a study comparing 28 days of injection of either heparin or a LMWH (dalteparin), the rats treated with standard heparin showed a significant reduction in osteoid surface and mineral apposition rates, and seven of eight rats suffered spontaneous femoral fractures. In contrast, the rats treated with the LMWH showed minimal decreases in bone indices and no fractures.²⁴ Variable effects have been shown with different LMWH formulations. In one study, fondaparinux was shown to have higher mitochondrial activity and protein synthesis in osteoblasts compared to enoxaparin and unfractionated heparin.¹⁰ While LMWH may not produce osteoporosis to the same extent as standard heparin, concern remains regarding the effect of LMWH on bone healing. At supertherapeutic doses, LMWH has been shown to decrease cancellous bone volume as demonstrated by a lack of normal remodeling and repair in an in vitro bone nodule assay.²⁵ Supertherapeutic doses have also been shown to decrease the osteoid surface area and to decrease alkaline phosphatase activity in a dose-dependent manner.²⁶

Because LMWH has a faster onset of action compared to warfarin, it is not surprising that a higher rate of surgical site hematomas has been observed with the use of LMWH in total hip arthroplasty.²⁷ The early use of LMWH in patients with fractures may presumably lead to a larger fracture site hematoma. It is generally accepted that fracture site hematoma plays a beneficial role in fracture healing. Mizuno et al. has shown that fracture site hematoma has osteogenic potential.²⁸ Several studies have shown that evacuation of this hematoma can be deleterious on fracture healing, especially when performed several days following fracture after the inflammatory phase has ended.^{29,30} In contrast, Street et al. has shown that the high potassium concentration of fracture site hematoma is cytotoxic to endothelial cells and osteoblasts.³¹ Only after these cytotoxic elements undergo resorption can the angiogenic and osteogenic cytokines present in fracture hematoma function. Brighton and Hunt have described an area of architectural disruption and cell degradation that diminishes with the distance from the hematoma.³² Therefore, increased fracture site hematoma volume may have deleterious effects on fracture healing. Whereas in this study we were unable to quantify fracture hematoma volume, we did not observe any detrimental impact of short term administration of LMWH on fracture healing.

This study has a number of limitations. Since the optimal duration of prophylaxis following trauma is undefined, we arbitrarily chose 14 days of LMWH administration to model its short term prophylactic use following pelvic or lower extremity trauma. We did not perform a dose-response study examining higher doses of dalteparin. The dose of dalteparin used in this study was based on the standard human dose and adjusted for animal weight. However, because of differences in metabolism, a higher dose may be required to obtain equivalent antithrombotic efficacy.³³ The standard prophylactic dose of dalteparin is 5,000 units daily, which for a 70-kg adult is approximately 70 units/kg. In comparison, Street et al., using a rabbit model, selected a daily enoxaparin dose of 2 mg, which based on animal weight was roughly 1 mg/kg. That dose is somewhat greater than the standard daily prophylactic enoxaparin dose of 40 mg, which equates to 0.57 mg/kg for a standard 70-kg adult. We did not evaluate any coagulation parameters during the study to determine what effect, if any, the administered dose of dalteparin was having on the animals coagulation system. We were also unable to quantify the size of fracture site hematoma to determine whether this was effected by the administration of dalteparin. While we examined the histology qualitatively, we did not perform a quantitative histomorphometric analysis of the fracture callus. In the prior study, in which LMWH was found to delay fracture repair, enoxaparin was used, whereas in this investigation, we used dalteparin.¹ While low molecular weight heparins have a similar mechanism of action, minor variations between the different available products could affect their impact on fracture healing. Finally, there is no evidence that our standard rat femur fracture model offers any

applicability to human fracture healing.

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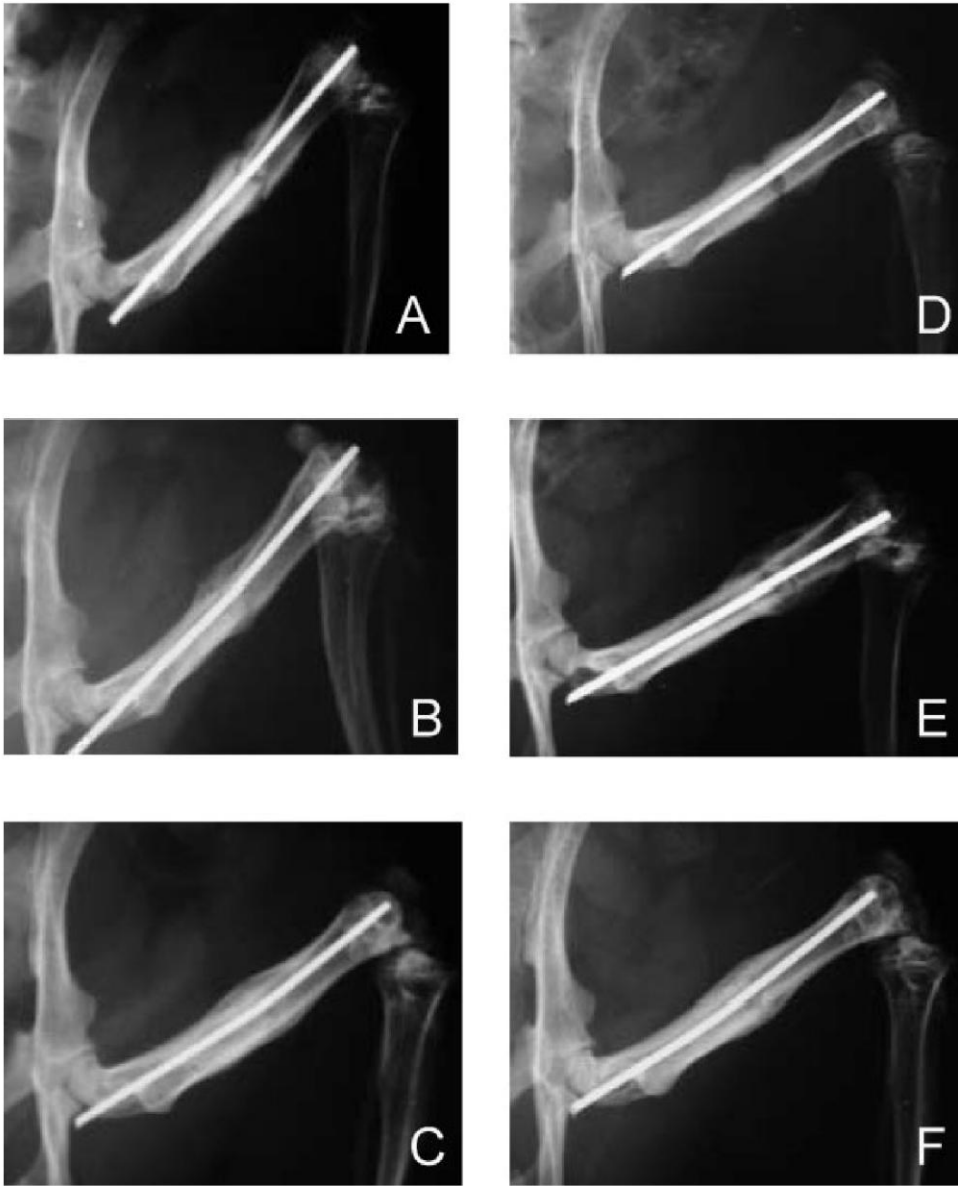


Figure 1. Representative radiographs of controls (A–C) and LMWH-treated animals (D–F) obtained at 2 weeks (A, D), 3 weeks (B, E), and 6 weeks following surgery (C, F).

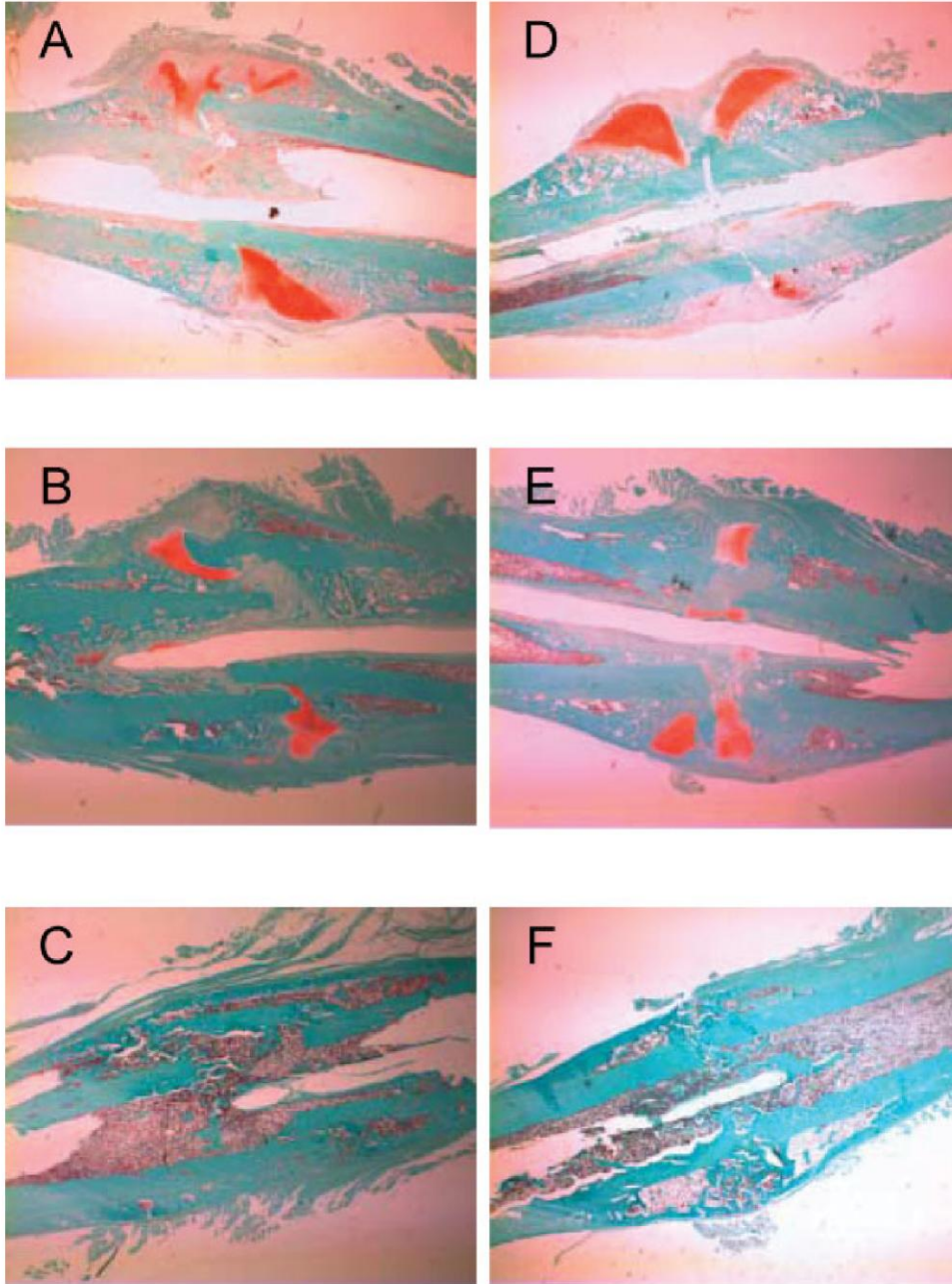


Figure 2. Representative histological sections of controls (A–C) and LMWH-treated animals (D–F) at 2 weeks (A, D), 3 weeks (B, E), and 6 weeks (C, F). A similar pattern of fracture healing was seen in the control and LMWH groups.

Table 1. Mechanical Test Values and Standard Deviations of Fractured and Intact Femurs at 2, 3, and 6 Weeks

Time from Fracture	Specimen and Sample Size	Maximum Torque to Failure (Nm)	Stiffness (Nm/rad)	Energy Absorption to Maximum Torque (Nm rad)
2 weeks	Control—fracture ($n = 7$)	0.077 ± 0.036	0.217 ± 0.109	0.016 ± 0.012
	Control—intact ($n = 7$)	0.360 ± 0.049	2.157 ± 0.952	0.039 ± 0.011
	LMWH—fracture ($n = 10$)	0.110 ± 0.052	0.505 ± 0.396	0.024 ± 0.026
	LMWH—intact ($n = 10$)	0.313 ± 0.090	1.683 ± 0.0500	0.055 ± 0.025
3 weeks	Control—fracture ($n = 8$)	0.156 ± 0.054	0.795 ± 0.485	0.030 ± 0.015
	Control—intact ($n = 8$)	0.403 ± 0.037	3.292 ± 0.831	0.042 ± 0.012
	LMWH—fracture ($n = 8$)	0.125 ± 0.056	0.695 ± 0.559	0.018 ± 0.013
	LMWH—intact ($n = 8$)	0.348 ± 0.82	2.084 ± 0.828	0.035 ± 0.009
6 weeks	Control—fracture ($n = 9$)	0.285 ± 0.094	2.020 ± 1.700	0.030 ± 0.015
	Control—intact ($n = 9$)	0.461 ± 0.052	2.390 ± 0.858	0.057 ± 0.013
	LMWH—fracture ($n = 8$)	0.343 ± 0.111	2.113 ± 1.177	0.042 ± 0.019
	LMWH—intact ($n = 8$)	0.402 ± 0.049	2.638 ± 1.336	0.042 ± 0.009

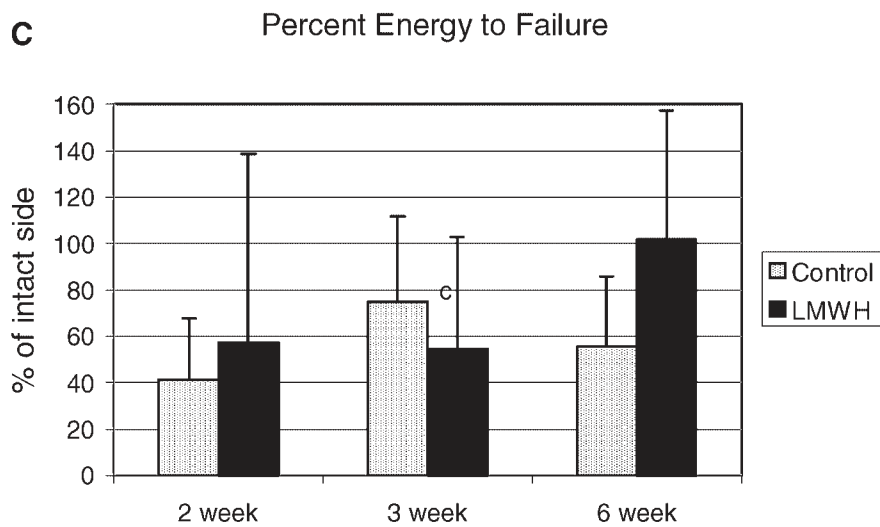
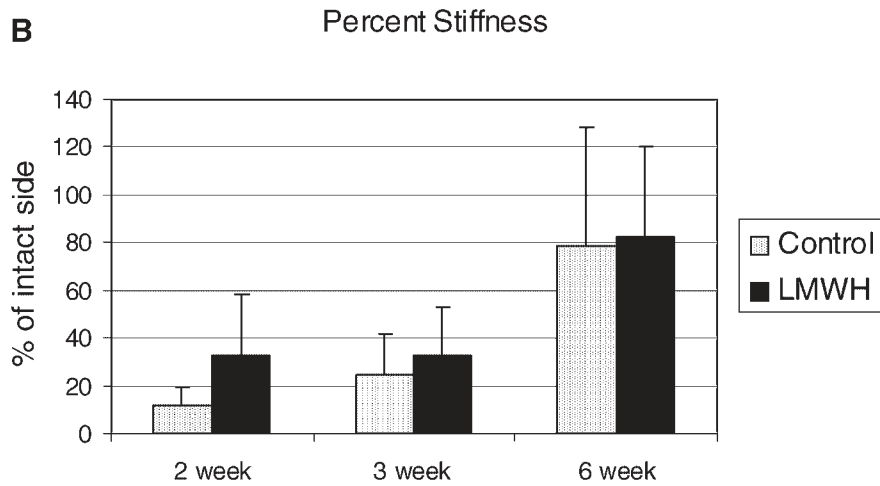
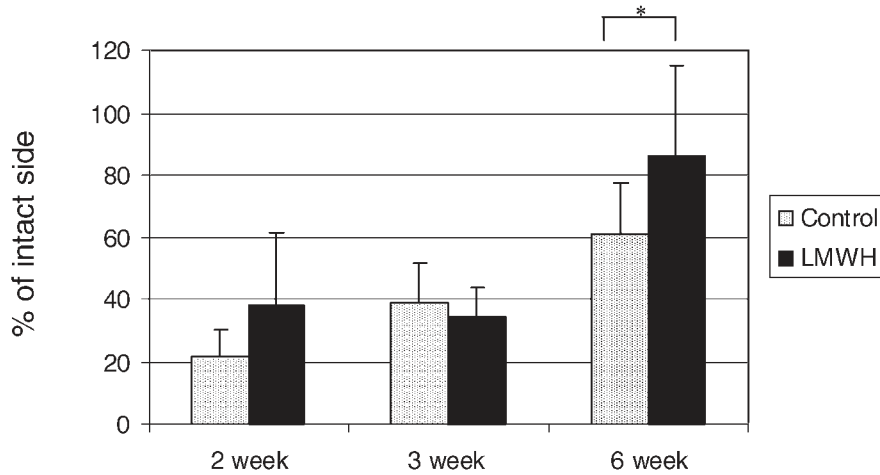


Figure 3. Biomechanical properties of the control and LMWH group normalized by the respective values of the intact femurs. (A) Percent maximum torque (maximum torque to failure of fractured femur/nonfractured intact femur $\times 100$). (B) Percent stiffness (stiffness of fractured femur/nonfractured intact femur $\times 100$). (C) Percent energy (energy absorption to maximum torque/nonfractured intact femur $\times 100$). The only significant difference between the LMWH and control groups was seen in the percent maximum torque at 6 weeks ($*p = 0.0072$).