ORIGINAL ARTICLE

Fixation augmented with micro-fragmented adipose derived stem cells (ORIF+) in simultaneous bilateral femoral shaft fracture: A pilot study

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ABSTRACT

Background and aim: Simultaneous bilateral femoral shaft fractures are extremely rare, high-energy injuries often associated with multiple systemic traumas. Intramedullary nailing remains the gold standard for diaphyseal femoral fixation, but alternative strategies may be required in complex or contraindicated cases. This pilot study aimed to assess the feasibility of open reduction and internal fixation biologically augmented with micro-fragmented adipose-derived stem cells (ORIF+) and to evaluate the reliability of the Radiographic Union Score (RUS) as a tool to monitor bone healing in simultaneous bilateral femoral fractures.

Received: 5 October 2025 | Accepted: 1 December 2025

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Methods: Data from seven patients (14 femurs) with simultaneous bilateral femoral shaft fractures treated between 2016 and 2020 were analyzed. Each patient underwent intramedullary fixation in one limb and ORIF+ in the contralateral limb. Clinical outcomes were assessed using the Visual Analog Scale (VAS) for pain, and radiographic healing was quantified using the RUS on serial radiographs obtained postoperatively and at 1, 3, 6, and 12 months, then annually. The correlation between RUS and VAS was analyzed statistically.
Results: All patients achieved complete bone union without complications. Both RUS and VAS scores showed progressive and significant improvement during follow-up. ORIF+ demonstrated higher RUS values and lower VAS scores at 3 and 6 months, suggesting enhanced early bone healing and pain control. Strong inter-observer agreement was observed for radiographic assessments ($\kappa > 0.85$).
Conclusions: Open reduction and plate fixation augmented with micro-fragmented adipose-derived stem cells appears to be a safe and feasible biological alternative for managing complex femoral shaft fractures in selected cases. The Radiographic Union Score proved to be a reliable, reproducible, and objective method for assessing bone healing in this setting. Larger multicentric studies are needed to confirm these preliminary findings. (www.actabiomedica.it)

Key words: fracture healing, delay union, RUS, ORIF augmented: ADSCs

Introduction

Simultaneous bilateral femoral shaft fractures (SBFSF) are unusual injuries typically resulting from high-energy trauma and are often associated with multiple injuries (1). These fractures are characterized by high morbidity and mortality rates and are prone to delayed union or non-union (2,3). Currently, intramedullary nailing is considered the gold standard for the treatment of femoral shaft fractures. Recent analyses comparing different treatment options have clearly shown that intramedullary fixation is associated with the lowest complication rates and reduced risk of loss of reduction compared with external fixation or plating techniques (4). A novel strategy, Open Reduction and Internal Fixation biologically augmented with micro-fragmented adipose-derived stem cells (ORIF+), may offer advantages in selected cases where intramedullary nailing is contraindicated or technically not feasible (4). Recent studies have demonstrated that adipose-derived stem cells (ADSCs) possess osteogenic and angiogenic potential through the secretion of paracrine factors that stimulate local bone regeneration, vascularization, and modulation of inflammation (5). Micro-fragmented adipose tissue (MFAT), obtained by mechanical processing of lipoaspirated fat without enzymatic manipulation, maintains a perivascular niche rich in regenerative cells and bioactive molecules (6). In orthopedic applications, ADSC-based augmentation has shown encouraging results in the management of nonunions and critical-size bone defects, suggesting its possible benefit also in acute long bone fractures. Given the critical role of fracture healing in determining patient outcomes and guiding follow-up, reliable and valid assessment methods are essential. However, fracture healing assessment remains highly subjective, and a universally accepted gold standard is lacking, leading to the absence of a univocal definition of fracture union (7). This lack of consensus in the orthopedic and radiological literature has led to the development of radiographic scoring systems to standardize the interpretation of plain X-rays (8). The Radiographic Union Score (RUS) has been applied in femoral shaft fractures to improve agreement between orthopedic surgeons and radiologists regarding fracture healing assessment. This scoring system provides a systematic approach that may assist both treatment planning and clinical follow-up, offering an objective and reproducible tool to assess bone healing over time, reducing subjectivity in radiographic evaluation (7,8). The aim of this pilot study was therefore

to assess the feasibility and potential value of RUS in monitoring bone healing in patients with simultaneous bilateral femoral shaft fractures treated with traditional intramedullary nailing versus ORIF+. The authors' hypothesis is that even if ORIF is not the gold standard for this type of fracture, it can still offer good results if enhanced with biological stimuli, as the use of local micro-fragmented adipose-derived stem cells.

Material and methods

Between January 2016 and May 2020, a total of 230 patients with femoral shaft fractures were surgically treated across three trauma centers. Among them, seven patients met the inclusion criteria for this pilot observational study.

Inclusion criteria: adult patients with simultaneous bilateral femoral shaft fractures (SBFSF), life expectancy > 6 months, and ability to provide informed consent.

Exclusion criteria: osteoporosis; hematologic or oncologic diseases; acute or chronic infections; previous lower limb trauma; nerve or vascular injuries; fractures not classified as AO type 32 (7); age <18 years, >65 years for males or >50 years for females; bone metabolism disorders; skeletal immaturity; neurological or psychiatric disorders; ipsilateral femoral neck fracture; lower limb amputation or sub-amputation; definitive external fixation; and abdominal or thoracic trauma precluding safe adipose tissue harvesting.

All femoral shaft fractures were classified according to the AO/OTA system (9) and the Winquist and Hansen classification (10). All patients initially underwent emergency damage control orthopedics. Definitive fixation was subsequently performed with either intramedullary nailing (IMN) or ORIF+. The mean time to definitive surgery differed between the groups, with no statistical difference ($p<0.05$). The inability to treat both femurs simultaneously on the same day was due to the significantly increased rate of postoperative anemia; therefore, based on the skin and general condition, the femur that would have required open reduction was postponed. This temporal difference was considered a potential confounding factor in the comparative analysis.

Harvesting and application of micro-fragmented adipose-derived stem cells (ADSCs)

In the ORIF+ group, autologous adipose tissue was harvested from the abdominal subcutaneous fat through a minimally invasive liposuction technique using a 20 mL syringe and a blunt cannula after local infiltration with Klein's solution. The lipoaspirate was mechanically processed using a closed sterile system (Lipogems® device), without enzymatic manipulation, to obtain micro-fragmented adipose tissue rich in perivascular stromal cells. The micro-fragmented suspension was applied intraoperatively around the fracture site immediately after definitive fixation and before wound closure, without the use of any scaffold or carrier. As already reported, patients with abdominal or thoracic trauma were excluded from the ORIF+ group due to contraindication to abdominal fat harvesting.

Radiographic and clinical evaluation

Fracture healing was evaluated through standard anteroposterior and lateral radiographs of both femoral shafts obtained preoperatively, postoperatively, and at 1, 3, 6, and 12 months of follow-up, and then annually. Two independent observers analyzed the radiographs, and disagreements were resolved by consensus (11). Pain was assessed using the Visual Analog Scale (VAS) (12) on the same day as radiographic examinations. Radiographic union was assessed using the Radiographic Union Score (RUS) as described by Chiavaras et al (13). Each cortex (anterior, posterior, medial, and lateral) was scored from 1 to 3 based on bridging callus, cortical continuity, and fracture line visibility, with a total score ranging from 10 to 30. At the time of radiographic union, selected cases also underwent CT evaluation to confirm cortical continuity. The minimum follow-up was 24 months, and the mean clinical follow-up was 28.8 ± 7.2 months. Partial weight bearing was allowed at 6 weeks postoperatively and progressed to full weight bearing between 10 and 12 weeks, according to radiographic evidence of callus formation. No postoperative infections or implant failures were recorded.

Statistical analysis

Descriptive statistics were used to summarize demographic and clinical characteristics. Continuous variables were expressed as mean ± standard deviation (SD) and compared using the *t*-test. Categorical variables were analyzed with the Chi-square test or Fisher's exact test when appropriate. Statistical significance was set at $p < 0.05$. The Pearson correlation coefficient (r) was calculated to explore relationships between VAS and RUS scores, while regression analysis assessed predictive trends over time. Inter-rater agreement between observers was evaluated using Cohen's kappa coefficient (κ). All analyses were performed using MedCalc Statistical Software, version 14.8.1 (MedCalc Software bvba, Ostend, Belgium).

Ethical considerations

This investigation was conducted in accordance with the Declaration of Helsinki and current national regulations. Given the retrospective analysis of prospectively collected data and the minimal-risk nature of the procedures, formal ethical committee approval was waived. Written informed consent was obtained from all participants for data collection and anonymous use for scientific purposes.

Results

A total of seven patients (14 femurs) met the inclusion, comprising five males and two females. The mean age was 33.7 ± 13.9 years (range 18–52), and the mean clinical and radiographic follow-up was 26.9 ± 5.2 months (range 24–30). Six of the seven patients were polytrauma cases, while one sustained isolated bilateral femoral fractures. Motor vehicle accidents represented the most common injury mechanism, followed by high falls (Table 1). No postoperative infections, implant failures, or reoperations occurred in either group. In the IMN group, two cases (28.6%) of gluteus medius heterotopic ossification were observed, both asymptomatic. No complications were reported in the ORIF+ group. At the final follow-up, all patients were fully weight-bearing and able to walk without aids.

Radiographic and clinical findings

According to the AO classification, fragmentary segmental fractures were the most frequent pattern, while type IV was the most common according to the Winquist and Hansen classification. Postoperative reduction was anatomic in six ORIF+ cases and satisfactory in one, while in the IMN group, four reductions were anatomic and three satisfactory (Table 2). The mean time to radiographic bone healing was 114.4 ± 14.2 days (range 96–132) for ORIF+ and 94.3 ± 4.1 days (range 87–98) for IMN group ($p < 0.05$). Radiographic assessment confirmed progressive cortical bridging and trabecular consolidation in all fractures. A representative case was documented in Figure 1. The use of CT evaluation in selected cases confirmed cortical continuity.

Correlation between RUS and VAS

The VAS scores demonstrated a statistically significant and progressive decrease throughout follow-up, paralleling radiographic healing. At 3 and 6 months, the ORIF+ limbs showed significantly lower pain levels compared with IMN group. RUS values exhibited a similar trend, with significantly higher scores for ORIF+ at both 3 and 6 months postoperatively. In the IMN group, a further significant increase in RUS was recorded between 6 and 12 months, suggesting delayed but complete healing. Regression analysis in the ORIF+ group showed an $r^2 = 0.054$ at 3 months and $r^2 = 0.067$ at 6 months ($p < 0.05$). In the IMN group, $r^2 = 0.007$ at 3 months and $r^2 = 0.225$ at 6 months ($p < 0.05$). Thus, a stronger correlation between RUS and VAS was observed in the ORIF+ group, indicating consistency between radiographic and clinical recovery trends.

Inter-observer reliability

During the follow-up, inter-observer agreement between radiographic alignment and bone healing was high in both groups, with Cohen's $\kappa = 0.90 \pm 0.05$ (range 0.82–0.99) in the ORIF+ group and $\kappa = 0.89 \pm 0.07$ (range 0.81–0.96) in the IMN group ($p > 0.05$).

Table 1. Characteristics of subjects undergoing to simultaneous bilateral femoral shaft fracture.

Patient	Sex	Age (yrs)	F-up (months)	Occupation	Associated Injury	Injury Mechanism	Closed or Open Fracture	Fracture Type According AO[7]	Fracture Type According Winquist and Hansen[8]
1	F	22	30	Student	None	High Fall Suicide	R Closed L Closed	R: Oblique L: Fragmentary segmental	R: 0 L: IV
2	M	18	28	Student	Polytrauma	MCV	R Open L Closed	R: Fragmentary segmental L: Transverse	R: III L: I
3	M	44	26	Carpenter	Polytrauma	MCV	R Closed L Closed	R: Fragmentary segmental L: Wedge fragmentary fractures	R: IV L: II
4	M	26	24	Farmer	Polytrauma	MCV	R Open L Open	R: Transverse L: Fragmentary segmental	R: I L:III
5	F	48	28	Metal Workman	Polytrauma	High Fall Suicide	R Open L Closed	R: Wedge fragmentary L: Fragmentary segmental	R: II L: III
6	M	52	24	Track Driver	Polytrauma	MCV	R Closed L Closed	R: Fragmentary segmental L:Oblique	R:IV L: I
7	M	27	32	Student	Polytrauma	MCV	R Closed L Closed	R: Fragmentary segmental L: Spiral	R: IV L: I

Abbreviations: F: female; L: Left; M: male; MVC: motor vehicle crash; R: Right.

Discussion

Simultaneous bilateral femoral shaft fractures are rare and severe injuries, typically caused by high-energy trauma and frequently associated with multiple systemic complications. These cases carry a significantly higher risk of morbidity and mortality compared with unilateral fractures, mainly due to the combined effects of hemodynamic instability, pulmonary embolic phenomena, and inflammatory overactivation (2,3). Intramedullary nailing (IMN) remains the gold standard for femoral shaft fixation, but its use may be limited in patients with polytrauma, narrow medullary canals, or concomitant injuries that contraindicate reaming or prolonged intramedullary manipulation (14). In such scenarios, open reduction and internal fixation (ORIF) could be considered as an alternative, particularly if biologically enhanced with regenerative strategies such as micro-fragmented adipose-derived stem cells (ADSCs) (15). Adipose-derived stem cells have demonstrated osteogenic and angiogenic potential through the secretion of growth factors and cytokines that promote bone formation, angiogenesis, and modulation of the inflammatory response (16,17). Mechanically processed micro-fragmented adipose tissue (MFAT) preserves a perivascular niche rich in stromal vascular fraction components without enzymatic alteration, maintaining cell viability and bioactive paracrine activity (18). In orthopedic and trauma settings, ADSC-based augmentation has shown encouraging results

Table 2. Peri surgery device, surgical outcomes and follow-up.

Patient	Damage Control Device	Days To Attend ORI+ surgery	Days To Attend IMN surgery	X-Rays Reduction ORIF+	X-Rays Reduction IMN	Radiographic Bone Healing In Days ORIF+	Radiograèhic Bone Healing In Days IMN	Radiographic Complication
1	External Fixation	14	7	Anatomic	Satisfactory	113	96	None
2	External Fixation	18	10	Satisfactory	Anatomic	134	98	None
3	External Fixation	12	9	Anatomic	Satisfactory	104	87	Bone Metaplasia Gluteus Medius in IM
4	External Fixation	11	8	Anatomic	Satisfactory	103	99	None
5	External Fixation	12	7	Anatomic	Anatomic	127	95	Bone Metaplasia Gluteus Medius in IM
6	External Fixation	15	10	Anatomic	Anatomic	124	93	None
7	External Fixation	22	11	Anatomic	Anatomic	96	92	None

Abbreviations: IMN: intramedullary nailing; ORIF+: Open Reduction and Internal Fixation augmented with micro-fragmented adipose-derived stem cells.

in both animal models and early clinical applications involving bone defects and nonunions (5,6,19,20). The present study aimed to explore the feasibility of ORIF biologically augmented with micro-fragmented ADSCs (ORIF+) in the management of SBFSF, using the Radiographic Union Score (RUS) as an objective and reproducible tool to quantify bone healing progression. Despite the small sample size, results demonstrate that both RUS and VAS scores improved progressively throughout follow-up, reflecting consistent radiographic and clinical recovery. Interestingly, patients treated with ORIF+ showed significantly higher RUS values and lower VAS scores at 3 and 6 months postoperatively compared with the contralateral limbs treated with IMN. All definitive surgical procedure were performed on patients in stable clinical conditions, according to the window of opportunity, and after a period of intensive care. When it was not possible to perform the double procedure simultaneously on the same day, the skin and general condition determined which femur to operate first (IMN) and which to postpone and subsequently definitively treat with ORIF+. Importantly, despite the likely delayed fixation with ORIF+, no complications, infections, or implant failures were recorded, and all patients achieved full functional recovery at final follow-up. The authors' hypothesis is confirmed: in fact, these findings suggest that the biological augmentation provided by micro-fragmented ADSCs may contribute to more efficient early bone remodeling and pain control in diaphyseal fractures. The RUS proved to be a reliable and practical tool to objectively monitor bone healing over time. The high inter-observer agreement ($\kappa > 0.85$) confirmed its reproducibility and its utility in standardizing radiographic evaluation, as previously reported by Chiavaras et al. (13) and Deppe et al. (7). The correlation between RUS and VAS scores observed in this study also highlights the relationship between radiological consolidation and pain reduction, supporting the integration of radiographic scoring with patient-reported outcomes in future studies. The main strength of this investigation lies in its design, where each patient served as their own control: one limb treated with conventional fixation and the contralateral with ORIF+. This

Figure 1. A 18 years old man reported a bilateral femoral shaft fracture (A, B); the follow up at 12 months show the bone healing (C, D).

unique condition minimizes inter-patient variability in systemic and biological healing capacity, providing a reliable internal comparison model. However, several limitations must be acknowledged. The small cohort size limits the statistical power and generalizability of the results. The heterogeneity of fixation techniques (IMN vs plate) and the variability in time to surgery may represent confounding factors. Furthermore, CT

evaluations were not uniformly performed across all cases. For these reasons, the present study should be interpreted as a pilot feasibility study, designed to generate hypotheses and explore the potential benefits of biological augmentation rather than to establish clinical superiority.

Conclusion

The use of standardized scoring systems such as RUS and VAS allowed for objective monitoring of bone healing and clinical improvement, confirming that ORIF+ lead to satisfactory clinical and radiographic outcomes comparable to intramedullary fixation in the tratment of simultaneous bilateral femoral shaft fractures. Given the small cohort and the feasibility nature of this study, these findings should be interpreted with caution. However, they provide a possible path for further multicentric studies with larger cohorts, standardized imaging protocols, and functional outcome measures to validate both these preliminary findings, and to better define indications, safety, and long-term benefits of ADSCs-enhanced fixation in trauma orthopedics.

Ethic approval: For this type of study is not required any statement relating to studies on humans and animals. All patients gave the informed consent prior being included into the study. All procedures involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments

Conflict of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

Consent for publication: All patients were informed in a clear and comprehensive way of the three types of treatments and other possible surgical and conservative alternatives. In the surgical consent was reported that clinical data can be used for scientific studies but remain anonymous. The manuscript contains no individual patient's information, nor identifiable images.

Authors' contributions: This manuscript is the result of a collaborative effort. G.R., A.S.: conception, methodology, writing; M.R. and P.Q: software, validation; P.Q, F.L. and F.D.M.: investigation; A.F., M.C, G.C, G.M.: resources; L.M.: data curation, A.F, G.R: supervision; L.M, G.R, A.F.: writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Availability of data and material: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration on the use of AI: No artificial intelligence tools were used in the drafting of the paper, neither for bibiographical research nor for the production of images/tables

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