Original Article

Journal of Iranian Medical Council, Volume 9, Issue no. 4
http://dx.doi.org/10.18502/jimc.v9i4.22469

Comparison of Bone Fracture Healing in Patients with Delayed Union of the Diaphyseal Femur and Tibia Shaft, with and without the Administration of Teriparatide

Arash Aris[1]* and Mahsa Babakhani Sangari[2]

1. Department of Orthopedics, Orthopedic Research Center, Poursina Hospital, Faculty of Medicine, Guilan University of Medical Sciences, Rasht, Iran
2. Department of Orthopedics, School of Medicine, Orthopedic Research Center, Trauma Institute, Poursina Hospital, Guilan University of Medical Sciences, Rasht, Iran

*** Corresponding author**
Arash Aris, MD
Department of Orthopedics, School of Medicine, Orthopedic Research Center, Trauma Institute, Poursina Hospital, Guilan University of Medical Sciences, Rasht, Iran
Tel: +98 9123031189
Fax: +98 13 3355 9787
Email: Eris@gums.ac.ir

Received: 26 Mar 2025
Accepted: 10 Sept 2025

Citation to this article
Aris A, Babakhani Sangari M. Comparison of Bone Fracture Healing in Patients with Delayed Union of the Diaphyseal Femur and Tibia Shaft, with and without the Administration of Teriparatide. *J Iran Med Counc.* 2026;9(4):994-1000.

Abstract

Background: This study investigates the effect of teriparatide on the healing of long bone fractures in the lower limbs of patients with delayed union. Fractures are a major global health issue, leading to increased mortality and economic costs.

Methods: This retrospective observational study with a one-year follow-up examined patients with delayed union of long bone fractures in the lower limbs who were treated with Teriparatide. The study followed these patients for one year to assess the effects and side effects of this treatment. Patient data, including age, gender, fracture type, and medical history were extracted from hospital archives using a standard checklist. Data analysis was conducted using SPSS version 22, and patients with incomplete records were excluded from the study.

Results: The present study showed that the average age of patients receiving Teriparatide administration was 42.37±13.63 years, whereas the average age of patients in the group without Teriparatide administration was 32.95±14.84 years. The results indicated no statistically significant difference in fracture healing between patients treated with teriparatide and those without the drug ($p>0.05$).

Conclusion: Radiographic evaluations in this study did not demonstrate a significant acceleration in fracture healing with the administration of Teriparatide. No adverse effects were reported among patients receiving the drug, supporting its favorable safety profile. While the study design and sample size limit the findings, they may contribute to informing future treatment strategies for managing delayed fracture healing.

Keywords: Diaphysis, Fracture healing, Non-union fractures, Parathyroid hormone, Tibia fractures

Introduction

Bone fractures are a global health problem that, in addition to morbidity and mortality, also has high economic costs (1). These costs include hospitalization, surgery, and long-term care after a fracture (2). The problem can occur at any age, but with increasing age and decreasing bone density, the risk of fractures increases, especially in the elderly. Sedentary lifestyles and increased life expectancy are also reasons for the increased prevalence of fractures in older populations (3). Bones naturally can heal themselves, but in severe cases, such as delayed union, this ability is limited, and alternative treatments are needed (4). Although bone grafting is traditionally used in cases of delayed union, its limitations have prompted exploration of pharmacological approaches such as parathyroid hormone therapy. However, this study does not aim to compare these two interventions directly (5).

One such alternative is the Parathyroid Hormone (PTH), which, in addition to helping with calcium and phosphorus metabolism, can also be effective in bone healing (5). Studies have shown that intermittent stimulation of PTH can increase bone formation, while continuous stimulation may lead to bone resorption (6,7). Teriparatide (PTH 1-34), a recombinant form of PTH, has been particularly effective in treating osteoporosis and has significantly improved fracture healing (8,9). Animal studies and some human research suggest that this hormone can speed up fracture healing and improve bone structure (10,11). However, additional studies, particularly in human patients, are still required to fully confirm the effect of teriparatide on the healing of specific fractures, such as diaphyseal femoral and tibial fractures (12,13). Given the importance of bone healing and the widespread use of the parathyroid hormone in cases of suspected delayed union, in this study, the aim was to investigate the effect of this drug on the healing of long bone fractures of the lower extremities and suggest optimal treatment strategies.

Materials and Methods

This study employed a retrospective observational cohort design to evaluate the association between Teriparatide administration and fracture healing outcomes in patients with delayed union of long bone diaphyseal fractures. Although not a randomized controlled trial, the study aimed to explore potential correlations between treatment and radiographic as well as clinical endpoints.

Patients were selected through convenience sampling from the orthopedic records of a referral hospital in 2022. All eligible individuals with complete clinical and radiographic follow-up data for at least six months' post-injury were included, in order to reduce selection bias. Patients with comminuted fractures were excluded due to their complex healing behavior and variable surgical protocols.

Definitions and diagnostic criteria

Delayed union was defined as the absence of bridging callus formation on radiographs at 3 months' post-fracture, accompanied by persistent pain and inability to bear weight. Non-union was defined as the lack of radiographic progression toward healing by 6 months, confirmed independently by two orthopedic surgeons. Bone union was considered achieved only when both clinical and radiographic criteria were fulfilled. Clinical union: no pain at the fracture site during weight-bearing or palpation. Radiographic union: bridging callus formation across at least three out of four cortices on anteroposterior and lateral X-rays.

Participants and treatment protocol

Inclusion criteria were: age between 18 and 65 years, delayed union of diaphyseal femoral or tibial shaft fractures persisting beyond three months and fracture classification (open/closed; spiral, oblique, or transverse pattern). Exclusion criteria included a history of radiotherapy, chemotherapy, malignancy, pregnancy, use of immunosuppressive medications, or incomplete medical records.

Patients who demonstrated no evidence of healing at three months were prescribed Teriparatide (20 μg/day, subcutaneously) for up to four months, following clinical guidelines and prior research indicating peak osteogenic activity within that timeframe. Monthly clinical visits were scheduled to evaluate pain, callus formation, and weight-bearing capacity. Adherence was assessed through self-report and appointment compliance. No patients discontinued therapy due to adverse effects.

Data collection

Demographic variables (age, gender), fracture-related variables (location, pattern, type), medical history (including diabetes mellitus), and social history (including smoking) were extracted using a standardized data collection form. Medication and supplement use were reviewed where documented, but due to incomplete records, this variable could not be analyzed comprehensively and is noted as a limitation.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 24.0 (IBM Corp., Armonk, NY, USA). Independent t-tests were applied to compare continuous variables (*e.g.*, age). Chi-square tests or Fisher's exact tests were used for categorical comparisons (*e.g.*, fracture type, healing outcome). Descriptive statistics included mean, standard deviation, frequency, and percentage. A p-value < 0.05 was considered statistically significant.

Results

A total of 40 patients with delayed union of femur or tibia shaft fractures were included in the study. Of these, 19 patients received Teriparatide (intervention group) and 21 did not (control group). The Teriparatide group consisted of 13 males and 6 females, while the control group included 17 males and 4 females. The mean age in the teriparatide group was 42.37±13.63 years, compared to 32.95±14.84 years in the control group, with the age difference being statistically significant (p=0.044). Table 1 showed that although the percentage of women in the Teriparatide group was higher than in the control group, this difference was not statistically significant (p=0.361). However, the mean age in the Teriparatide group was significantly higher than in the non-Teriparatide group (p=0.044). The comparison of fracture type and pattern between the two groups (Table 2) indicated that the type of fracture (open or closed) was not significantly associated with Teriparatide administration (p=0.698). However, there was a statistically significant

Table 1. Comparison of age and gender between groups with and without Teriparatide administration

Variable	Teriparatide administered (N=19)	Teriparatide not administered (N=21)	p-value
Gender	N(%)	N(%)	
Female	6(31.58%)	4(19.05%)	0.361*
Male	13(68.42%)	17(80.95%)	
Age (Mean±SD)	42.37±13.63	32.95±14.84	0.044**
Age (Min, Max)	(21.0, 64.0)	(18.0, 65.0)	

*Chi-square test, **Independent t-test.

Table 2. Comparison of fracture type and pattern between groups with and without Teriparatide administration

Variable	Teriparatide administered (N=19)	Teriparatide not administered (N=21)	p-value
Fracture type	N(%)	N(%)	
Closed	16(84.21%)	16(76.19%)	0.698
Open	3(15.79%)	5(23.81%)	
Fracture pattern			
Transverse	11(57.89%)	12(57.14%)	
Oblique	6(31.58%)	1(4.76%)	0.035*
Spiral	2(10.53%)	8(38.10%)	

*Fisher's exact test.

Table 3. Comparison of fixation methods between groups with and without Teriparatide administration (Revised)

Fixation method	Teriparatide administered (N=19)	Teriparatide not administered (N=21)
Plate and screws	6	7
Intramedullary nail (IMN)	4	3
External fixator	1	3
Other (Combined)	3	5

Footnote: "Plate" and "Plate & Screws" were merged into a single category titled "Plate and Screws" to reflect standard orthopedic classification. The category "Pin" was excluded as it is not recognized as an independent fixation method for diaphyseal fractures. All patients underwent internal fixation (plate, screw, IMN) or external fixation based on fracture characteristics and clinical protocols. "Other (Combined)" refers to cases where two or more fixation methods (*e.g.*, IMN+Plate) were used concurrently.

Table 4. Comparison of fracture healing and Teriparatide side effects between groups

Variable	Teriparatide administered (N=19)	Teriparatide not administered (N=21)	p-value
Fracture healing (Radiographic)	N(%)	N(%)	
Union	10(52.63%)	10(47.62%)	0.999
Non-union	7(36.84%)	8(38.10%)	
Callus Formation	2(10.53%)	3(14.29%)	
Teriparatide side effects			
Yes	0(0.00%)	-	-
No	19(100.00%)	-	-

*Fisher's exact test.

difference in fracture patterns between the groups (p=0.035), with oblique fractures being more common in the Teriparatide group. The evaluation of fixation methods used for fractures (Table 3) revealed no statistically significant association between fixation methods and Teriparatide administration (p=0.878). Furthermore, the assessment of radiographic healing, defined as bridging callus formation in at least three cortices, was observed in 52.63% of patients receiving Teriparatide and 47.62% in the control group. Clinical healing (based on pain resolution and restored weight-bearing) was consistent with radiographic findings in all but two patients (Table 4), indicating no significant difference in healing rates between the two groups (p=0.999). Additionally, no adverse effects were reported in the Teriparatide group. The analysis of participants' patient records was reviewed for clinical variables known to influence fracture healing, including diabetes mellitus, smoking status, and history of steroid use. These factors were included in the statistical analysis (Table 5) showed no statistically significant association between these factors and teriparatide administration (p=0.698 and p=0.603, respectively).

Table 5. Comparison of past medical history and social history between groups

Variable	Teriparatide administered (N=19)	Teriparatide not administered (N=21)	p-value
Past Medical History (PMH)			
Yes	3(15.79%)	5(23.81%)	0.698
No	16(84.21%)	16(76.19%)	

Contd. table 5.

Social History (SH)			
None	13(68.42%)	12(57.14%)	
Smoking	2(10.53%)	4(19.05%)	
Opium	0(0.00%)	1(4.76%)	0.603
Full addiction	0(0.00%)	2(9.52%)	
Opium & smoking	3(15.79%)	2(9.52%)	
Methadone	1(5.26%)	0(0.00%)	

Footnote: smoking and substance use (opium, methadone) are categorized under social history, not medical history.

Discussion

This study did not demonstrate a statistically significant effect of Teriparatide on fracture healing in patients with delayed union; however, due to design limitations, no definitive conclusions can be drawn.

Teriparatide, as an anabolic agent, has shown potential in promoting bone regeneration by stimulating osteoblast activity and enhancing callus formation through intermittent PTH signaling (14,15). While its efficacy is well-established in osteoporosis management, its role in fracture healing, particularly in cases of delayed union, remains inconclusive. This study aimed to explore this application in a clinical setting; however, findings did not demonstrate a significant difference in radiographic healing outcomes between patients who received Teriparatide and those who did not. Several confounding factors, including age differences and variability in fracture patterns, may have influenced the results. The lack of observed benefit could also reflect limitations in treatment duration, adherence, or the timing of teriparatide initiation. Furthermore, although callus formation was monitored radiographically, subtle histological or metabolic changes may have gone undetected due to the imaging methods employed (16).

Several confounding factors, including age differences and variability in fracture patterns, may have influenced the results. The lack of observed benefit could also reflect limitations in treatment duration, adherence, or the timing of teriparatide initiation. Furthermore, although callus formation was monitored radiographically, subtle histological or metabolic changes may have gone undetected due to the imaging methods employed. The present study results are consistent with those of Eastman *et al* (17). who reported no significant acceleration of healing with PTH analogs despite some improvement in function. Similarly, studies by Kanakaris *et al* and Johansson *et al* (18) reported that while PTH analogs improved functional outcomes across various fractures, it did not accelerate healing. Johansson *et al* and Kanakaris *et al* further confirmed Teriparatide's lack of effect on fracture healing (19,20). However, Lou *et al* (21) demonstrated that Teriparatide significantly improved fracture healing and functional outcomes in osteoporotic women. Peichl *et al* (22) also found that PTH accelerated hip fracture healing, reducing the mean recovery time from 12.6 weeks to 7.8 weeks ($p \leq 0.001$). Further large-scale, randomized studies are recommended to better understand the therapeutic potential of teriparatide in bone healing.

The influence of medications and supplements such as corticosteroids, vitamin D, and calcium on fracture healing is well documented. However, due to inconsistent documentation in medical records, these variables could not be reliably analyzed in the current study and remain a notable limitation. Additionally, the observed variability in Teriparatide response underscores the need for individualized treatment strategies based on fracture characteristics, patient age, bone quality, and timing of intervention.

To address these challenges, future research should employ prospective, controlled designs with standardized treatment protocols, earlier initiation of therapy, and the use of advanced imaging or biochemical markers for more accurate assessment of bone healing processes.

Given the retrospective design, limited sample size,

and absence of randomization, the current findings should be interpreted with caution. This study does not provide definitive evidence regarding the efficacy or inefficacy of teriparatide in delayed union. Larger randomized controlled trials are necessary to draw more reliable and generalizable conclusions.

Conclusion

In this retrospective observational study, Teriparatide did not demonstrate a statistically significant effect on fracture healing outcomes in patients with delayed union. No adverse effects were reported among treated patients, suggesting a favorable safety profile. However, due to key limitations including the non-randomized design, small sample size, and potential selection bias the findings should be interpreted with caution. To determine the true therapeutic efficacy of Teriparatide in fracture healing, well-designed randomized controlled trials with larger cohorts and standardized protocols are essential.

Ethics approval and consent to participate

This study received approval from the research council at Guilan University of Medical Sciences. [IR.GUMS.REC.1403.135].

Funding

This research was not funded.

Acknowledgement

The researchers thank the Guilan University of Medical Sciences and Razi Clinical Research Development Unit, and the nurses who participated in the study. This study received approval from the research council at Guilan University of Medical Sciences. [IR.GUMS.REC.1403.135].

Conflict of Interest

There was no conflict of interest in this manuscript.

References

1. Camal Ruggieri IN, Cícero AM, Issa JPM, Feldman S. Bone fracture healing: perspectives according to molecular basis. J Bone Miner Metab 2021;39:311-31.

2. Bergh C, Wennergren D, Möller M, Brisby H. Fracture incidence in adults in relation to age and gender: a study of 27,169 fractures in the Swedish Fracture Register in a well-defined catchment area. PloS One 2020;15(12):e0244291.

3. Henriksen K, Karsdal MA, John Martin T. Osteoclast-derived coupling factors in bone remodeling. Calcif Tissue Int 2014;94(1):88-97.

4. Della Rocca GJ, Crist BD, Murtha YM. Parathyroid hormone: is there a role in fracture healing? J Orthop Trauma 2010;24 Suppl 1:S31-S5.

5. Amizuka N, Davidson D, Liu H, Valverde-Franco G, Chai S, Maeda T, et al. Signalling by fibroblast growth factor receptor 3 and parathyroid hormone-related peptide coordinate cartilage and bone development. Bone 2004;34(1):13-25./

6. Ban Z-N, Li Z-J, Gu Q-S, Cheng J, Huang Q, Xing S-X. Correlation of serum PTH level and fracture healing speed in elderly patients with hip fracture. J Orthop Surg Res 2019;14:1-3.

7. Shi HF, Xiong J, Chen YX, Wang JF, Qiu XS, Huang J, et al. Comparison of the direct and indirect reduction techniques during the surgical management of posterior malleolar fractures. BMC Musculoskelet Disord 2017 Mar 14;18(1):109.

8. Xu Y, Lv C, Zhang J, Li Y, Li T, Zhang C, et al. Intermittent parathyroid hormone promotes cementogenesis in a PKA and ERK1/2 dependent manner. J Periodontol 2019;90(9):1002-13.

9. Chen T, Wang Y, Hao Z, Hu Y, Li J. Parathyroid hormone and its related peptides in bone metabolism. Biochem Pharmacol 2021;192:114669.

10. Sain A, Bansal H, Pattabiraman K, Sharma V. Present and future scope of recombinant parathyroid hormone

therapy in orthopaedics. J Clin Orthop Trauma 2021;17:54-8.

11. Iwata A, Kanayama M, Oha F, Hashimoto T, Iwasaki N. Effect of teriparatide (rh-PTH 1–34) versus bisphosphonate on the healing of osteoporotic vertebral compression fracture: A retrospective comparative study. BMC Musculoskelet Disord 2017;18(1):148.

12. Kirker-Head CA. Recombinant bone morphogenetic proteins: novel substances for enhancing bone healing. Vet Surg 1995 Sep-Oct;24(5):408-19.

13. Mason DR, Renberg WC. Postsurgical enhancement of fracture repair: biologic alternatives to bone grafting. Compendium. 2001.

14. Andreassen TT, Ejersted C, Oxlund H. Intermittent parathyroid hormone (1–34) treatment increases callus formation and mechanical strength of healing rat fractures. J Bone Miner Res 1999;14(6):960-8.

15. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster J-Y, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344(19):1434-41.

16. Peivandi MT, Bagheri F, Birjandi Nezhad A, Amel Farzad S, Jarahi L, Esmail Zade M, et al. Efficacy of Parathyroid Hormone on Diaphysis Delayed-: union: and Non-: union: Fractures of Tibia/Fibula in shahid kamyab hospital in 97-98. Iranian Journal of Orthopedic Surgery 2021 Feb 19;19(1):7-11.

17. Shi Z, Zhou H, Pan B, Lu L, Liu J, Kang Y, et al. Effectiveness of teriparatide on fracture healing: a systematic review and meta-analysis. PLoS One 2016;11(12):e0168691.

18. Eastman K, Gerlach M, Piec I, Greeves J, Fraser W. Effectiveness of parathyroid hormone (PTH) analogues on fracture healing: a meta-analysis. Osteoporos Int 2021:1-16.

19. Kanakaris NK, West RM, Giannoudis PV. Enhancement of hip fracture healing in the elderly: evidence deriving from a pilot randomized trial. Injury 2015;46(8):1425-8.

20. Johansson T. PTH 1-34 (teriparatide) may not improve healing in proximal humerus fractures: a randomized, controlled study of 40 patients. Acta Orthopaedica 2016;87(1):79-82.

21. Lou S, Lv H, Wang G, Zhang L, Li M, Li Z, et al. The effect of teriparatide on fracture healing of osteoporotic patients: a meta analysis of randomized controlled trials. BioMed Research International 2016;2016(1):6040379.

22. Peichl P, Holzer LA, Maier R, Holzer G. Parathyroid hormone 1-84 accelerates fracture-healing in pubic bones of elderly osteoporotic women. J Bone Joint Surg Am 2011;93(17):1583-7.