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Review Article

# Teriparatide and Atrophic Nonunion

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**Abstract**

Fracture healing is a complex biological process orchestrated by a delicate interplay of cellular and molecular mechanisms. While the majority of fractures heal spontaneously with appropriate treatment, challenging cases, such as atrophic nonunion, may require adjunctive therapies to achieve successful bone regeneration. In recent years, teriparatide has gained attention as a promising bone-forming agent with the potential to enhance fracture healing and improve clinical outcomes. Preclinical studies using animal models of bone injury have provided evidence supporting the efficacy of teriparatide in promoting fracture healing and resolving nonunion. Histological and radiological findings show that teriparatide enhances callus formation, accelerates bone remodeling, improves biomechanical properties, and reduces the incidence of healing complications. These preclinical results highlight the potential of teriparatide as a therapeutic agent for managing atrophic nonunion in clinical practice. However, further research is necessary to address the limitations of current studies and to establish evidence-based guidelines for the use of teriparatide in nonunion management.

**Keywords:** Atrophic nonunion, Bone Regeneration, Fracture Healing, Parathyroid Hormone, Teriparatide

## Introduction

Fracture healing is a well-orchestrated process involving the interplay of biomechanics and biology, leading to the formation and remodeling of bone tissue. However, in some cases, this process lacks coordination, resulting in delayed or failed fracture healing.

As life expectancy rises globally, the incidence of fractures is expected to increase accordingly. While most fractures typically undergo uncomplicated healing, delayed union or nonunion occurs in approximately 5-10% of cases, with variability depending on factors such as anatomical location, fracture type, and patient age[1]. The rising prevalence of nonunion is linked to improved survival rates following major trauma observed in recent years. Despite often being associated with aging, nonunion is most commonly observed between the ages of 35 and 44, with a higher incidence among males[2].

Delayed bone healing and nonunion pose significant challenges for orthopedic surgeons nowadays. In addressing these issues, alongside conventional surgical approaches, there is growing interest in the potential use of anabolic therapy with teriparatide.

## Definition and Characteristics of Atrophic Nonunion

Nonunion is defined as a fracture persisting for at least nine months without evident signs of healing for three consecutive months[3]. After this timeframe, bone bridging is absent, signaling a complete halt in bone regeneration. An alternative definition covers fractures that continue to exhibit symptoms and demonstrate no potential for healing without intervention

Nonunion is divided into two main categories: septic and aseptic, based on the presence of infection. Aseptic nonunions are further classified into hypertrophic, atrophic, and oligotrophic types. Hypertrophic nonunions are marked

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by robust callus formation but insufficient bridging and stability. Atrophic nonunions, in contrast, exhibit reduced callus formation, localized suppression of osteogenesis, and inadequate blood supply to the affected area. Hypertrophic nonunions generally indicate favorable local biology, while atrophic nonunions suggest unfavorable biological conditions[4].

Atrophic nonunion often represents a prolonged delay in the natural healing process of fractures. Unlike hypertrophic nonunion, characterized by an excess of callus tissue, atrophic nonunion typically shows minimal or absent callus formation . This deficiency reflects an interruption in the biological cascade of bone healing[5]. Radiographically, atrophic nonunion exhibits persistent fracture lines, minimal bridging callus, and sclerosis at the fracture ends, indicating reduced biological activity and inadequate remodeling. Patients with atrophic nonunion may experience persistent pain, limited mobility, and instability at the fracture site, significantly impacting their quality of life and often requiring further intervention[6]. Several factors contribute to atrophic nonunion, including poor vascularization, inadequate fracture stabilization, underlying medical conditions like osteoporosis or diabetes, and patient-related factors such as advanced age or smoking. Histological examination reveals diminished osteoblastic activity and an abundance of fibrous tissue, confirming the atrophic nature of the nonunion[7].

## Pathophysiology of Atrophic Nonunion

Multiple physiological mechanisms contribute to fracture nonunion. Firstly, compromised blood supply diminishes the fracture's healing capacity, consequently reducing osteogenic cell activity. Secondly, injury to the osteoconductive scaffold hampers new bone formation, often due to the increased distance required for bone healing. Thirdly, underlying pathological biological processes not only impede blood flow but also disrupt the production of essential growth factors necessary for bone healing. Additionally, inadequate mechanical stability at the fracture site can impede the healing process. Should any of these processes be adversely affected, the risk of nonunion significantly rises. From a biological perspective, the primary cause of nonunion often stems from inadequate revascularization and angiogenesis in the fracture site. Nonunion cases resulting from compromised biology, characterized by impaired revascularization, require further interventions to enhance their biological capacity to achieve bone bridging and the formation of a functional bone structure[8,9].

## Factors Contributing to Atrophic Nonunion

Adequate blood supply is essential for delivering oxygen, nutrients, and osteogenic cells to the fracture site, facilitating the healing process. Atrophic nonunion often occurs in regions with compromised vascularity, such as in the presence of segmental fractures, soft tissue injury, or vascular damage. Insufficient blood flow leads to ischemia, impairing cellular metabolism and inhibiting the recruitment of reparative cells[7].

Inadequate stabilization of the fracture fragments prevents mechanical stability, disrupting the formation of a functional callus and impeding the bone healing process. Biological instability may result from inadequate fracture reduction, implant failure, or excessive interfragmentary motion, leading to micromotion at the fracture site and nonunion formation[10].

Persistent inflammation at the fracture site interferes with the normal healing process and contributes to the development of atrophic nonunion. Chronic inflammation stimulates the production of pro-inflammatory cytokines, such as interleukin-1 and tumor necrosis factor-alpha, which inhibit osteoblastic activity, promote fibrous tissue formation, and impair bone regeneration[11].

Underlying metabolic conditions, such as osteoporosis, diabetes mellitus, and malnutrition, compromise the bone healing process and increase the risk of atrophic nonunion. Metabolic disturbances alter the balance between bone formation and resorption, leading to reduced osteogenic potential and impaired bone quality. Additionally, medications such as corticosteroids and nonsteroidal anti-inflammatory drugs may negatively impact bone healing and contribute to nonunion formation[10].

## Implications

Nonunion, while relatively rare, can have significant implications for patients. Surgical intervention is often necessary to address nonunion, although this may lead to further complications and the need for additional surgical procedures. Nonunion can result in chronic pain, functional impairment preventing weightlifting or the resumption of usual activities, joint stiffness, secondary osteoarthritis, and psychological distress[12]. Moreover, high-risk groups, such as individuals with spinal cord injuries, may experience additional complications such as pressure ulcers, osteomyelitis, and the possibility of subsequent amputation[13]. Alongside traditional surgical methods, there is increasing interest in systemic anabolic therapy with teriparatide to address these issues. Nonoperative treatments of nonunion can be quite effective. The goal of managing atrophic nonunion is to address both the biological and mechanical stability factors.

## Teriparatide

Teriparatide, also known as recombinant human parathyroid hormone (1-34), is a synthetic analog of the biologically active fragment of parathyroid hormone (PTH). Approved for the osteoporosis treatment, teriparatide exerts its pharmacological effects primarily through its action on osteoblasts[14]. Acting as an anabolic agent, teriparatide boosts osteoblastic activity, resulting in increased cancellous and cortical bone mass, thereby improving bone structure. Unlike antiresorptive agents like bisphosphonates, which hinder bone resorption, teriparatide enhances bone turnover

by activating osteoblasts and promoting the production of osteoid, the bone's organic matrix[15]. Through the stimulation of osteoblast precursor proliferation and differentiation, teriparatide expedites the formation of new bone tissue, enhancing the skeleton's structural integrity[16].

## Teriparatide's Role in Fracture Healing: Mechanisms and Benefits

Teriparatide primarily induces bone formation by targeting osteoblasts, the cells responsible for generating and mineralizing new bone tissue. It achieves this through several key mechanisms:

1. **Osteoblastogenesis Stimulation**: Teriparatide binds to PTH receptors on osteoblasts, triggering intracellular signaling pathways that promote osteoblast proliferation and differentiation. This results in an increased population of active osteoblasts, thereby boosting bone formation and hastening the healing process[17].
2. **Bone Matrix Synthesis Enhancement**: Teriparatide prompts osteoblasts to produce and deposit osteoid, the primary organic matrix of bone composed mainly of collagen. By augmenting osteoid synthesis, teriparatide creates a framework for mineralization and facilitates the formation of new bone tissue[18].
3. **Bone Turnover Induction**: Teriparatide stimulates bone turnover by enhancing both bone formation and resorption. Initially, teriparatide treatment may cause a temporary increase in bone resorption, but this is subsequently followed by a more prolonged and significant increase in bone formation, ultimately leading to a net gain in bone mass over time[19].
4. **Wnt Signaling Pathway Activation**: Teriparatide activates the Wnt signaling pathway, which is a crucial regulator of bone formation and remodeling. This pathway is essential for osteoblast differentiation, proliferation, and function. The activation of the Wnt signaling pathway by teriparatide significantly contributes to its anabolic effects on bone tissue[20].

Teriparatide provides several benefits in fracture healing[21]:

1. It accelerates callus formation by stimulating osteoblast proliferation and differentiation, facilitating earlier bridging of the fracture gap.
2. By enhancing bone turnover and synthesizing new bone tissue, it improves the mechanical properties and structural integrity of healed fractures, reducing the risk of recurrence.
3. Teriparatide enhances biomechanical properties by increasing bone mineral density, trabecular connectivity, and cortical thickness, thereby improving fracture resistance and load-bearing capacity.
4. It may reduce healing complications such as delayed union or nonunion by promoting a robust healing response, which is particularly advantageous in challenging cases like atrophic nonunion.

## Teriparatide and Nonunion

Beyond teriparatide's established role in osteoporosis management, it has garnered interest as a potential therapeutic agent for promoting fracture healing in challenging clinical scenarios, including atrophic nonunion. Current findings suggest that teriparatide accelerates fracture healing by enhancing the biomechanical properties of the callus and expediting the recruitment and differentiation of chondrocytes, which are crucial steps in the initial stages of endochondral ossification[22,23]. Teriparatide, while effective in promoting bone healing, may present some common side effects. These can include hyperuricemia, nausea, dizziness, headache, leg cramps, and injection site reactions such as redness or pain. While these side effects are generally mild and manageable, patients should be aware of them when considering teriparatide treatment for nonunion fractures[24].

Based on the gold standard treatment for atrophic nonunion, the revision of fixation should incorporate aspects of osteoconduction, utilizing scaffolds and optimizing mechanical conditions, and osteoinduction, employing bone grafts, bone morphogenetic proteins, and enhancing vascularity[25]. The "diamond concept" emphasizes the equal importance of mechanical stability and the biological environment in promoting successful bone repair responses. Crucial elements required for effective non-union therapy include vascularity, osteoinductive factors, osteogenic cells, osteoconductive matrix, and mechanical stability[26]. However, in some instances surgical intervention may not be viable due to patient-related or technical limitations. Therefore, thorough investigation is needed to explore teriparatide as a potential alternative to revision surgery for the treatment of atrophic nonunion.

In accordance with established principles of nonunion management[27], it is acknowledged that hypertrophic nonunions primarily result from inadequate mechanical stability rather than compromised biological bone healing potential. Thus, when callus formation is present, addressing mechanical instability becomes the primary focus to achieve bone union. In contrast, atrophic nonunions, characterized by minimal or absent callus, require the stimulation of bone healing processes. The utilization of teriparatide for treating atrophic nonunions is recommended. However, it's essential to recognize that while teriparatide may offer benefits, it cannot entirely overcome significant biomechanical or local biological challenges, such as non-contact between fragments or the presence of deperiosted bone fragments.

Furthermore, infected nonunions constitute a unique subset of impaired bone healing. In the presence of untreated infection, relying solely on teriparatide treatment for achieving bone healing is impractical. Instead, adhering to the principles of debridement, bone grafting, and antibiotic therapy remains crucial in managing infected nonunions[28].

When evaluating the effectiveness of teriparatide for nonunion treatment, caution is warranted. While randomized controlled trials in humans are lacking, case reports and

**Table 1.** Case studies and series reporting effective management of atrophic nonunion using teriparatide (SC: Subcutaneous injection).

| Authors | Type of Study | Number of Subjects | Age (In Years) | Dosage And Duration of Teriparatide | Type of Fracture | Treatment Outcome | Mean Time to Union |
|---|---|---|---|---|---|---|---|
| Tsai et al. (2019)[29] | Case report | 1 | 60 | A daily SC injection of 20μg was administered for 6 months | Femur shaft fracture | After 3 months, X-rays revealed bone bridges and a reduced gap between the fracture fragments | 11 months |
| Mancilla et al. (2015)[57] | Case series | 6 | 19-64 | A daily SC injection of 20μg was administered for 3-9 months, discontinued upon radiographic evidence of fracture healing | Femoral and tibial shaft | Complete union was achieved in 3 to 9 months in 5 out of 6 patients | 6.4 months in 5 patients |
| Giannotti et al. (2013)[34] | Case report | 1 | 80 | A daily SC injection of 20μg was administered for 3 months | Distal femur metaphysis fracture | Complete union was achieved in 3 months | 3 months |
| Ochi et al. (2013)[59] | Case report | 1 | 74 | A weekly SC injection of 56.5 μg was administered for 6 months | Periprosthetic fracture | New bone filled the fracture gap after 5 months | 6 months |
| Mitani et al. (2013)[38] | Case report | 1 | 88 | A weekly SC injection of 56.5 μg was administered for 9 months | Femoral neck fracture | Complete union was achieved in 5 months | 5 months |
| Lee et al. (2012)[56] | Case series | 3 | 29-64 (mean 43.67) | A daily SC injection of 20μg was administered for 3-9 months | Femur neck and shaft fractures | The fractures completely healed between 6 and 12 months, with an average healing time of 8.7 months after treatment was discontinued | 13.7 months |
| Oteo-Alvaro et al. (2010)[58] | Case report | 1 | 32 | A daily SC injection of 20μg was administered for 5 months | Humeral shaft | Complete union was achieved in 5 months | 5 months |

case series have suggested a potential role of teriparatide in nonunion management (Table 1)[29–34]. However, because much of the literature comprises these reports, unsuccessful treatments may be underrepresented. Nonetheless, existing literature indicates a high union rate of approximately 95%[35].

The duration of teriparatide treatment until bone union varies significantly, with reported durations ranging from as short as two months to as long as nine months[36,37]. Deciding the optimal treatment duration hinges on factors such as the type of fracture and individual response to therapy. It's crucial to customize the treatment duration for each case. Given that teriparatide is approved for osteoporosis treatment for a maximum duration of 24 months, it's reasonable to apply this limit to nonunion treatment as well. This approach ensures the cautious use of the medication while aiming to maximize its therapeutic effects.

Canintika's review[35] affirmed the safety of teriparatide application in nonunion and delayed union cases. Although the standard dosage typically involves daily injections of 20 μg of teriparatide, some studies have investigated the viability of weekly injections as an alternative. This approach is particularly beneficial for patients who may have difficulty administering daily subcutaneous injections. Several studies examining teriparatide use for nonunion treatment have explored the option of weekly subcutaneous injections at a dosage of 56.5 μg[38,39].

Existing literature does not provide evidence suggesting that teriparatide is only

effective in certain bones. However, the increased incidence of nonunions following fractures of long bones likely contributes to the greater frequency of teriparatide use for nonunion treatment in these bones.

## Preclinical Evidence of Teriparatide in Nonunion

Animal studies have provided valuable insights into the potential effectiveness of teriparatide in promoting fracture healing and resolving nonunion.

Lin et al.[40] conducted a study to evaluate the efficacy of systemic administration of recombinant human parathyroid hormone (PTH 1–34) in preventing atrophic fracture nonunion in a murine model. Using a reproducible long-bone fracture nonunion model in mice, they compared daily intraperitoneal injections of PTH 1–34 with saline injections over a period of 14 days. Results indicated a significantly higher rate of bony union and reduced gap size in the PTH-treated group compared to controls. Histological analysis revealed cortical bridging with mature bone formation in PTH-treated subjects, suggesting improved healing through primary intramembranous ossification. These findings highlight the potential clinical relevance of PTH 1–34 in the management of atrophic fracture nonunions.

In the study of Perez Nunez et al.[41], despite prior evidence suggesting a positive effect of PTH on fracture healing, particularly in rat diaphysis fracture models, they did not observe any beneficial effects. Previous research has shown that PTH administration during fracture healing enhances callus volume and strength, stimulates osteogenic responses, and up-regulates gene markers associated with osteoblast differentiation[42–45]. However, the applicability of these findings to nonunion models, particularly with regards to the whole PTH molecule (1–84), remains uncertain. While their study administered the drug on a five-day-per-week regimen, contrary to the standard seven-day regimen, this alone does not explain the lack of positive results. Other studies have reported positive effects of PTH on fracture healing despite similar administration schedules[46]. Their findings align with previous research by Tagil et al.[47], who also found no beneficial effect of PTH therapy in a rat model of hypertrophic non-union. Thus, despite promising indications in fracture healing, the potential efficacy of PTH does not seem to translate consistently into non-union models. Further research is warranted to elucidate the specific mechanisms and conditions under which PTH or its analogs may exert therapeutic effects on fracture healing and nonunion.

In the study of Menger[48], mice with segmental bone defects received daily subcutaneous injections of either PTH 1–34 or saline. Analysis revealed that PTH-treated mice demonstrated markedly improved bone formation, increased bending stiffness, and a higher presence of osteoclasts and microvessels within the callus tissue. Additionally, PTH treatment reduced the inflammatory response in aged animals and upregulated the expression of key proteins associated with bone healing. These results suggest that PTH is an effective intervention for atrophic non-union formation in aged animals. In this research using a murine atrophic nonunion model, the main finding was that PTH treatment significantly enhances bone formation, resulting in successful osseous bridging within 10 weeks post-surgery. This enhancement in bone formation was accompanied by elevated bending stiffness and improved vascularization within the callus tissue of the femora in PTH-treated animals compared to controls. Given the clinical approval of PTH as a therapeutic agent, these results suggest its potential as a promising candidate for addressing non-union formation in elderly patients.

The study findings highlight the significant enhancement of atrophic non-union regeneration in aged mice following PTH treatment. This improvement correlates with an increased presence of osteoclasts and CD31-positive microvessels, along with heightened expression of COX-2 and PI3K within the callus tissue during the initial healing phase. Osteoclasts play a pivotal role in cartilage resorption and callus tissue remodeling, facilitating the development of mature bone tissue[49]. The observed increase in CD31-positive microvessels in PTH-treated mice suggests enhanced vascularization, supported by the substantial elevation in vascular endothelial growth factor (VEGF) expression. VEGF is a critical growth factor known to promote angiogenesis, a vital process in bone regeneration[50]. Additionally, the upregulation of COX-2 expression during the early inflammatory phase of repair indicates the role of PTH in modulating inflammatory mediators crucial for bone healing[51-53]. Furthermore, the significant increase in PI3K expression within the callus tissue of PTH-treated mice suggests a potential mechanism underlying PTH's enhancement of bone healing through the regulation of cellular metabolism and differentiation[54]. These findings collectively suggest that PTH treatment not only promotes vascularization but also directly stimulates bone tissue formation, offering valuable insights into potential therapeutic approaches for atrophic non-unions in aged individuals.

A study of Ma et al.[55] has unveiled a crucial mechanism underlying the effects of intermittent PTH treatment on fracture healing. We discovered that PTH treatment significantly increases intracellular cAMP concentrations, thereby activating the cAMP/PKA/CREB signaling pathway. This activation leads to an elevation in phosphorylated CREB levels, subsequently triggering the IHH signaling pathway. IHH, in turn, promotes increased chondrogenesis within the callus, accelerates chondrocyte maturation and mineralization, and ultimately expedites the fracture healing process. By elucidating this intricate signaling cascade, our investigation provides valuable insights into the mechanisms through which PTH treatment influences fracture repair. Furthermore, it sheds light on the impact of PTH on

biomarkers of endochondral ossification, paving the way for the identification of effective therapeutic targets for fracture management.

## Evidence from Clinical Cases

In 2020, a systematic review[35] identified 20 relevant articles involving 64 adult patients diagnosed with delayed union or nonunion fractures These studies, encompassing 15 case reports, 4 case series, and one prospective study, administered subcutaneous injections of teriparatide 20 μg/day for an average duration of 7.3 ± 1.5 weeks to 9.7 months. Remarkably, 95.3% of the subjects demonstrated complete fracture union without any observed adverse effects throughout the follow-up period, which extended from 3 to 24 months. The findings suggest that daily subcutaneous injection of teriparatide 20 μg may represent a promising and safe treatment option for nonunion fractures. Nonetheless, further clinical investigations are warranted to validate its safety and efficacy. The review underscored the necessity for additional data elucidating the efficacy of teriparatide in managing nonunions.

Tsa and Hu[29] reported a case involving a 60-year-old female who experienced a femoral shaft fracture. Following immediate closed reduction and internal fixation surgery, no evidence of healing was evident over a six-month period, prompting a diagnosis of atrophic nonunion. Subsequently, the patient underwent subcutaneous administration of teriparatide at a daily dosage of 20 μg for six months. Notably, complete union at the fracture site was achieved six months post-cessation of teriparatide treatment.

Giannotti et al.[34] presented a case report demonstrating the successful management of delayed union in a femoral fracture using teriparatide. The patient initially diagnosed with a distal metaphyseal femoral fracture post-total knee arthroplasty, underwent surgical intervention involving open reduction and internal fixation. However, radiological assessments at 5- and 7-month intervals post-surgery showed no evidence of healing. Subsequent administration of teriparatide treatment for two months resulted in radiographic evidence depicting the formation of bone bridges and a reduction in the gap between fragments, accompanied by the distinct appearance of newly formed bone tissue. Remarkably, complete healing was achieved after three months of teriparatide therapy. This case underscores the potential of teriparatide in inducing bone formation and expediting fracture healing, suggesting its viability as a therapeutic option for nonunion and delayed consolidation. Additionally, the study suggests the possibility of using teriparatide preventively or adjunctively in high-risk fracture cases and complex fractures in osteoporotic bone.

In their study, Lee et al.[56] administered teriparatide to three patients presenting with femoral nonunion subsequent to initial surgical intervention. The patients included a 38-year-old man with a femoral shaft fracture, a 64-year-old woman with a distal femoral fracture, and a 29-year-old man with a femoral neck fracture, all resulting from traffic accidents. Teriparatide treatment was administered for a duration of 3–9 months following the diagnosis of nonunion. Notably, all three patients achieved successful union without requiring further surgical intervention, and no adverse events associated with teriparatide use were reported. These findings suggest that teriparatide may serve as a feasible alternative to surgical intervention in cases of femoral nonunion.

A retrospective study[57] evaluated the effects of teriparatide on the healing process of long bone nonunion fractures. Six patients aged 19 to 64 years, presenting with tibial or femoral fractures characterized by atrophic nonunion unresolved for 3 to 36 months, underwent treatment with teriparatide at a dosage of 20 μg/day. Accelerated healing was observed in 5 out of 6 patients, resulting in complete union within a timeframe ranging from 3 to 9 months. Younger patients without comorbidities exhibited shorter recovery periods. Teriparatide treatment was well-tolerated. These findings indicate teriparatide as a promising therapeutic option for nonunion fractures; however, its efficacy may vary depending on associated comorbidities, highlighting the need for further exploration through randomized trials.

A 32-year-old male patient with a diaphyseal humeral fracture underwent surgical intervention. Despite 6 months passing with no clinical or radiographic evidence of union, successful healing was achieved through a single intervention involving the administration of teriparatide for 5 months. No adverse effects were reported[58].

An 88-year-old female with rheumatoid arthritis and a history of steroid use presented with a femoral neck fracture. The patient underwent surgical treatment and consented to receive therapy comprising a once-weekly injection of 56.5 μg chemically synthesized teriparatide. After 18 months post-surgery, a computed tomography scan following 20 consecutive weekly administrations of teriparatide revealed signs of healing. Complete fracture union was achieved at 23 months[38].

A case report by Ochi et al.[59] describes the case of a 74-year-old woman with rheumatoid arthritis who developed nonunion of a periprosthetic fracture following total knee arthroplasty. Despite undergoing internal fixation and bone grafting twice, bone union was not achieved. However, successful bone fusion occurred after six months of simple once-weekly administration of teriparatide. While this report is based on a single patient, it suggests the potential benefit of prophylactic teriparatide administration alongside surgical interventions for managing nonunion of periprosthetic fractures post-total knee arthroplasty.

## Conclusion

When a fracture exhibits signs of delayed healing or progresses to nonunion, it necessitates the utilization of all available treatment options, both surgical and non-surgical.

**Among the latter, anabolic support with teriparatide has demonstrated its effectiveness. With its potent bone-forming effects and favorable safety profile, teriparatide holds promise as a novel approach for enhancing fracture healing and resolving nonunion in challenging clinical scenarios such as management of atrophic nonunion. However, further research, particularly randomized trials, is essential to validate the drug's efficacy and establish a definitive treatment protocol.**

## *References*


1. Mills LA, Aitken SA, Simpson AHRW. The risk of non-union per fracture: current myths and revised figures from a population of over 4 million adults. Acta Orthop.2017;88(4):434–9.
2. Zura R, Xiong Z, Einhorn T, Watson JT, Ostrum RF, Prayson MJ, et al. Epidemiology of Fracture Nonunion in 18 Human Bones. JAMA Surg 2016;151(11):e162775.
3. Cunningham BP, Brazina S, Morshed S, Miclau T. Fracture healing: A review of clinical, imaging and laboratory diagnostic options. Injury 2017;48:S69–75.
4. Frölke JPM, Patka P. Definition and classification of fracture non-unions. Injury 2007;38:S19–22.
5. Harwood PJ, Ferguson DO. An update on fracture healing and non-union. Orthop Trauma 2015;29(4):228–42.
6. Brinker MR, Trivedi A, O'Connor DP. Debilitating Effects of Femoral Nonunion on Health-Related Quality of Life. J Orthop Trauma 2017;31(2):e37–42.
7. Brownlow HC, Reed A, Simpson AHR. The vascularity of atrophic non-unions. Injury 2002;33(2):145–50.
8. Calori GM, Giannoudis P V. Enhancement of fracture healing with the diamond concept: The role of the biological chamber. Injury 2011;42(11):1191–3.
9. Giannoudis P V., Jones E, Einhorn TA. Fracture healing and bone repair. Injury 2011;42(6):549–50.
10. Niikura T, Yang Lee S, Sakai Y, Nishida K, Kuroda R, Kurosaka M. Causative factors of fracture nonunion: the proportions of mechanical, biological, patient-dependent, and patient-independent factors. J Orthop Sci 2014;19(1):120–4.
11. Mills L, Tsang J, Hopper G, Keenan G, Simpson AHRW. The multifactorial aetiology of fracture nonunion and the importance of searching for latent infection. Bone Joint Res 2016;5(10):512–9.
12. Yeo JH, Kim JY. Surgical Strategy for Scaphoid Nonunion Treatment. J Hand Surg (Asian-Pacific Vol 2018;23(04):450–62.
13. Sinnott B, Ray C, Weaver F, Gonzalez B, Chu E, Premji S, et al. Risk Factors and Consequences of Lower Extremity Fracture Nonunions in Veterans With Spinal Cord Injury. JBMR Plus. 2022 Mar 5;6(3).
14. Blick SKA, Dhillon S, Keam SJ. Teriparatide: a review of its use in osteoporosis. Drugs 2008;68(18):2709–37.
15. Marin F, Ma YL. Teriparatide. In: Osteoporotic Fracture and Systemic Skeletal Disorders. Singapore: Springer Singapore; 2022. p. 339–59.
16. 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.
17. D'Amelio P, Tamone C, Sassi F, D'Amico L, Roato I, Patanè S, et al. Teriparatide increases the maturation of circulating osteoblast precursors. Osteoporos Int 2012;23(4):1245–53.
18. Wein MN, Kronenberg HM. Regulation of Bone Remodeling by Parathyroid Hormone. Cold Spring Harb Perspect Med 2018; 8(8):a031237.
19. Girotra M, Rubin MR, Bilezikian JP. The use of parathyroid hormone in the treatment of osteoporosis. Rev Endocr Metab Disord 2006;7(1–2):113–21.
20. Kulkarni NH, Halladay DL, Miles RR, Gilbert LM, Frolik CA, Galvin RJS, et al. Effects of parathyroid hormone on Wnt signaling pathway in bone. J Cell Biochem 2005;95(6):1178–90.
21. Cheng M, Gupta V. Teriparatide - Indications beyond osteoporosis. Indian J Endocrinol Metab 2012;16(3):343.
22. Kendler DL, Marin F, Zerbini CAF, Russo LA, Greenspan SL, Zikan V, et al. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet. 2018 Jan;391(10117):230–40.
23. Cipriano CA, Issack PS, Shindle L, Werner CML, Helfet DL, Lane JM. Recent Advances toward the Clinical Application of PTH (1-34) in Fracture Healing. HSS Journal® Musculoskelet J Hosp Spec Surg 2009;5(2):149–53.
24. Cranney A, Papaioannou A, Zytaruk N, Hanley D, Adachi J, Goltzman D, et al. Parathyroid hormone for the treatment of osteoporosis: A systematic review. CMAJ. Canadian Medical Association Journal. 2006.
25. Moghaddam A, Zietzschmann S, Bruckner T, Schmidmaier G. Treatment of atrophic tibia non-unions according to 'diamond concept': Results of one- and two-step treatment. Injury 2015;46:S39–50.
26. Andrzejowski P, Giannoudis P V. The 'diamond concept' for long bone non-union management. J Orthop Traumatol 2019;20(1):21.
27. Nauth A, Lee M, Gardner MJ, Brinker MR, Warner SJ, Tornetta P, et al. Principles of Nonunion Management: State of the Art. J Orthop Trauma 2018;32(3):S52–7.
28. Struijs PAA, Poolman RW, Bhandari M. Infected Nonunion of the Long Bones. J Orthop Trauma 2007;21(7):507–11.
29. Tsai M-H, Hu C-C. Teriparatide as nonoperative treatment for femoral shaft atrophic nonunion: A case report. World J Clin Cases 2019; 7(18):2838–42.
30. Sato M, Westmore M, Ma YL, Schmidt A, Zeng QQ, Glass EV, et al. Teriparatide [PTH(1–34)] Strengthens the Proximal Femur of Ovariectomized Nonhuman Primates Despite Increasing Porosity. J Bone Miner Res 2004;19(4):623–9.
31. Ismailidis P, Suhm N, Clauss M, Mündermann A, Cadosch D. Scope and Limits of Teriparatide Use in Delayed and Nonunions: A Case Series. Clin Pract 2021;11(1):47–57.
32. Pola E, Pambianco V, Colangelo D, Formica VM, Autore G, Nasto LA. Teriparatide anabolic therapy as potential treatment of type II dens non-union fractures. World J Orthop 2017;8(1):82.
33. Kundu S. Teriparatide treatment in fracture non-union: a case report. Int J Res Orthop 2017;
34. Giannotti S, Bottai V, Dell'Osso G, de Paola G, Pini E, Guido G. Atrophic femoral nonunion successfully treated with teriparatide. Eur J Orthop Surg Traumatol 2013;23(S2):291–4.
35. Canintika AF, Dilogo IH. Teriparatide for treating delayed union and nonunion: A systematic review. J Clin Orthop Trauma 2020;11:S107–12.
36. Matsumoto T, Ando M, Sasaki S. Effective treatment of delayed union of a lumbar vertebral fracture with daily administration of teriparatide in a patient with diffuse idiopathic skeletal hyperostosis. Eur Spine J 2015;24(S4):573–6.
37. Coppola C, Del Buono A MN. Teriparatide in Fracture Non-Unions. Transl Med UniSa 2014;12:47–53.
38. Mitani Y. Effective treatment of a steroid-induced femoral neck fracture nonunion with a once-weekly administration of teriparatide in a rheumatoid patient: a case report. Arch Osteoporos 2013;8(1–

2):131.
39. Tachiiri H, Okuda Y, Yamasaki T, Kusakabe T. Weekly teriparatide administration for the treatment of delayed union: a report of two cases. Arch Osteoporos 2014;9(1):179.
40. Lin EA, Liu C-J, Monroy A, Khurana S, Egol KA. Prevention of Atrophic Nonunion by the Systemic Administration of Parathyroid Hormone (PTH 1–34) in an Experimental Animal Model. J Orthop Trauma 2012;26(12):719–23.
41. Pérez Núñez MI, Ferreño Blanco D, Alfonso Fernández A, Casado de Prado JA, Sánchez Crespo M, De la Red Gallego M, et al. Comparative study of the effect of PTH (1–84) and strontium ranelate in an experimental model of atrophic nonunion. Injury 2015; 46(12):2359–67.
42. Andreassen TT, Fledelius C, Ejersted C, Oxlund H. Increases in callus formation and mechanical strength of healing fractures in old rats treated with parathyroid hormone. Acta Orthop Scand 2001; 72(3):304–7.
43. Nakajima A, Shimoji N, Shiomi K, Shimizu S, Moriya H, Einhorn TA, et al. Mechanisms for the Enhancement of Fracture Healing in Rats Treated With Intermittent Low-Dose Human Parathyroid Hormone (1–34). J Bone Miner Res 2002;17(11):2038–47.
44. Nakazawa T, Nakajima A, Shiomi K, Moriya H, Einhorn TA, Yamazaki M. Effects of low-dose, intermittent treatment with recombinant human parathyroid hormone (1–34) on chondrogenesis in a model of experimental fracture healing. Bone 2005;37(5):711–9.
45. Alkhiary YM, Gerstenfeld LC, Krall E, Westmore M, Sato M, Mitlak BH, et al. Enhancement of experimental fracture-healing by systemic administration of recombinant human parathyroid hormone (PTH 1-34). J Bone Jt Surg 2005;87(4):731–41.
46. Komatsubara S, Mori S, Mashiba T, Nonaka K, Seki A, Akiyama T, et al. Human parathyroid hormone (1–34) accelerates the fracture healing process of woven to lamellar bone replacement and new cortical shell formation in rat femora. Bone 2005;36(4):678–87.
47. Tägil M, McDonald MM, Morse A, Peacock L, Mikulec K, Amanat N, et al. Intermittent PTH(1–34) does not increase union rates in open rat femoral fractures and exhibits attenuated anabolic effects compared to closed fractures. Bone 2010;46(3):852–9.
48. Menger MM, Tobias AL, Bauer D, Bleimehl M, Scheuer C, Menger MD, et al. Parathyroid hormone stimulates bone regeneration in an atrophic non-union model in aged mice. J Transl Med 2023;21(1):844.
49. Bahney CS, Zondervan RL, Allison P, Theologis A, Ashley JW, Ahn J, et al. Cellular biology of fracture healing. J Orthop Res 2019; 37(1):35–50.
50. Keramaris NC, Calori GM, Nikolaou VS, Schemitsch EH, Giannoudis PV. Fracture vascularity and bone healing: A systematic review of the role of VEGF. Injury 2008;39:S45–57.
51. Naik AA, Xie C, Zuscik MJ, Kingsley P, Schwarz EM, Awad H, et al. Reduced COX-2 Expression in Aged Mice Is Associated With Impaired Fracture Healing. J Bone Miner Res. 2009 Feb 1;24(2):251–64.
52. Xie C, Ming X, Wang Q, Schwarz EM, Guldberg RE, O'Keefe RJ, et al. COX-2 from the injury milieu is critical for the initiation of periosteal progenitor cell mediated bone healing. Bone 2008;43(6):1075–83.
53. Peng H, Usas A, Olshanski A, Ho AM, Gearhart B, Cooper GM, et al. VEGF Improves, Whereas sFlt1 Inhibits, BMP2-Induced Bone Formation and Bone Healing Through Modulation of Angiogenesis. J Bone Miner Res 2005;20(11):2017–27.
54. Scanlon V, Walia B, Yu J, Hansen M, Drissi H, Maye P, et al. Loss of Cbl-PI3K interaction modulates the periosteal response to fracture by enhancing osteogenic commitment and differentiation. Bone 2017;95:124–35.
55. Ma C, Liu H, Wei Y, Li H, Miao D, Ren Y. Exogenous PTH 1-34 Attenuates Impaired Fracture Healing in Endogenous PTH Deficiency Mice via Activating Indian Hedgehog Signaling Pathway and Accelerating Endochondral Ossification. Front Cell Dev Biol 2022; 9:750878.
56. Lee Y-K, Ha Y-C, Koo K-H. Teriparatide, a nonsurgical solution for femoral nonunion? A report of three cases. Osteoporos Int 2012; 23(12):2897–900.
57. Mancilla EE, Brodsky JL, Mehta S, Pignolo RJ, Levine MA. Teriparatide as a Systemic Treatment for Lower Extremity Nonunion Fractures: A Case Series. Endocr Pract 2015;21(2):136–42.
58. Oteo-Álvaro Á, Moreno E. Atrophyc humeral shaft nonunion treated with teriparatide (rh PTH 1-34): A case report. J Shoulder Elb Surg 2010;19(7):e22–8.
59. Ochi K, Ikari K, Naomi A, Momohara S. Administration of teriparatide treatment for a challenging case of nonunion of periprosthetic fracture after total knee arthroplasty. Arch Osteoporos.2013;8(1–2):159.