# Histological Assessment of the Effect of Teriparatide Treatment on Mandibular Bone Defect Healing in Rats

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**Original Article**

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## ABSTRACT

**Introduction:** After injuries, infections, or tumor removal, bone rebuilding is necessary for endogenous healing. Among the several induced ways for repairing bone defects are the allogenic, synthetic, and autologous membrane techniques. However, surgical implantation of bone graft and bone infill materials at the bone defect location may cause edema, infection, and heterotopic bone growth. Therefore, osteogenic systemic medications will be an outstanding treatment of bone lesions.

**Aim of the Study:** This work aimed at evaluating the systemic effect of teriparatide on bone healing after surgical induction of bony defects in rats' mandibles.

**Materials and Methods:** In this study, 40 albino rats were separated into two groups (control and treatment groups) each including 20 rats. The same surgical procedure was performed on all rats. A hole was made in the mandible (3 mm in diameter and 3 mm in depth) and were left empty. Teriparatide was administered in a dosage of (10µg/kg) daily subcutaneous injection for the treated group. Animals were euthanized at four-time intervals (7, 14, 21 and 28) days. The mandibles were separated, sectioned preserved, and processed for histological analysis.

**Results:** The results revealed that there was an increase in new bone formation in short healing time in the teriparatide-treated group on the 7$^{th}$ day and 14th day of the experiment. The group treated with parathyroid hormone significantly exceeded the control group in the mean ranks of each osteoblast presence, osteoid matrix density and osteoid matrix mineralization. Also the treated group was significantly superior to the control group in woven bone islets formation on the 14$^{th}$, 21st, and 28th days of the experiment.

**Conclusion:** Rats that were treated with teriparatide exhibited enhanced bone production and maturation, as well as a reduced healing time, in comparison to the control rats, in relation to bone defects.

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**Key Words:** Bone defect healing, rats, teriparatide.

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## INTRODUCTION

Throughout a person's life, bone undergoes ongoing remodeling since it is a highly vascularized and dynamic natural composite. It has great load-bearing ability for locomotion and acts as a casing to protect sensitive internal organs, attributable to its high mechanical qualities and fracture toughness. Bone tissue is not solely vital for its structural roles, but also as an endocrine organ that regulates the homeostasis of minerals (particularly Ca and P ions) and nutrients on a global scale[1].

Bone healing is an intricate biological process that goes through specific regenerative patterns[2]. Bone healing can be classified into primary (direct) bone healing and secondary (indirect) bone healing. The healing is considered primary or direct when the gap is less than 0.1 mm, and the fracture site is stabilized[3].

The gap in this type of healing is filled by continuous ossification without connective or cartilaginous tissue, and no callus is formed[4]. The primary healing process occurs as a direct transition of mesenchymal cells to bone-forming osteoblasts through a process called intramembranous ossification[5].

Indirect bone healing occurs more commonly than direct bone healing[4]. It is associated with callus formation, includes endochondral and intramembranous bone formation, and similar to embryological bone development[6]. Indirect bone healing can be divided into four distinct phases. At first, the inflammatory phase occurs, then the second phase in which soft callus formation (cartilage form) and revascularization occur. The third phase is represented by hard callus formation (woven bone), and finally the last phase is the remodeling of bone[7].

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The osteoanabolic drug teriparatide (TPTD) is a recombinant human parathyroid hormone (rhPTH) used to treat osteoporosis in postmenopausal women, males with primary or hypogonadal osteoporosis, and those who have developed the condition as a result of using corticosteroids. The TPTD peptide consists of the first 34 amino acids derived from the human parathyroid hormone[8].

The variation in the impact of parathyroid hormone (PTH) on bone is attributed to variations in the dosage and timing of bone exposure to the hormone, and in instances of prolonged exposure to parathyroid hormone (PTH), such as in cases of hyperparathyroidism, bone resorption overcomes bone production. Conversely, intermittent exposure to low doses of PTH, such as via the daily injection of teriparatide, stimulates bone growth to a greater extent than bone resorption[9].

Therefore, this study aimed to investigate the effect of systemic teriparatide on rat mandible bone healing.

## MATERIAL AND METHODS

Forty male albino Sprague Dawley rats with a weight range of (300_350 gm) and ages of 6-7 months were used in the study. The animal lived at the animal house of college of dentistry, University of Mosul in special cages at temperatures (22±2) 0C. The animals were kept under standard conditions and given standard diet and water under the supervision of veterinary doctor to check the general health and condition of the animal before and after the surgical procedure.

### *Animal grouping*

Animals were divided into the control group (n=20) and the TPTD-treated group (n=20). Each group was subdivided into four groups, each one contained 5 rats according to the healing periods (7,14, 21, 28 days) postoperatively.

### *Surgical procedure*

The rat's weight was assessed using the electronic digital scale. After that, each animal was anesthetized by consecutive intraperitoneal injections of ketamine® (ketamine hydrochloride) 90mg/kg general anesthetic agent and xylazine® 10mg/kg sedative analgesic solution.

Using an electric hair clipper and a 10% povidone-iodine solution, the submandibular area of the animal was shaved while it was lying supine. Using scalpel blade number 15, we performed a 15-millimeter-long linear incision in the submandibular region of the rat's skin, parallel to the mandible's inferior border.

After the soft tissues had been dissected, the periosteum was elevated, utilizing Howarth periosteal elevator, and the mandibular bone was clearly seen, a hole of (3mm) in diameter and (3mm) in depth was created (5 mm) behind the last molar tooth using a portable dental engine with a straight hand piece and a rounded carbide bur at slow speed (2000 rpm) and a heavy stream of distilled water for irrigation. Dryness of the wound, suturing and disinfection were done.

### *Post-Surgical Procedure*

**Animal Care**

After surgery, the rats were placed in separated cages while recovery from anesthesia, then monitoring their feeding (soft standardized diet), physical activity were done by expert veterinarians. All rats returned to their activity and feeding usually 3 to 5 hours after surgery.

**Experimental substances**

For the TPTD-treated group, Teriparatide (Forsteo) was available in a form of an injection obtained from Turkey. Teriparatide 10 µg/kg was injected subcutaneously into the dorsal neck region and a needle was used to penetrate the skin overlying the shoulder, while the control group received nothing during the experiment scheduled time.

**Bone specimen preparation for histopathological examination**

Samples for histological studies were fixed in neutral buffer formalin (10%) for 48 hours to one week. All fixed specimens were washed in moderately flowing tap water for at least 30 minutes. Fixed samples were decalcified in formic acid (10%). It took 24 hours, several days, or even months, depending on the size of the specimens, then washing in phosphate buffer saline (PBS) was undertaken. Decalcified samples were dehydrated in ascending grades of ethanol (70%, 90%, and 100%), cleared in xylene, infiltrated, and embedded in paraffin wax. Using a microtome, serial sections of 5 microns were cut and stained with hematoxylin and eosin (H and E).

### *Histopathological examination*

The sections of the defected area of rat mandible were examined under light microscope by two blind pathologists to assess the following criteria; blood cast resolution, gap occlusion, areolar tissue deposition, osteoblast and osteoid matrix density, osteoid matrix mineralization and calcification at the center of the callus. Also Woven and trabecular bone islets, inflammatory foci, lamellar bone formation, original compact bone resorption and osteoclasts activity, as well as lamellar bone remodeling. Those criteria were determined by monitoring three different fields by the examiners at each section. The data were recorded for each criteria and scaled as 0, 1, 2, and 3 graduated according to their prominence and occurrence. The histological criteria were photographed by using digital AmScope MD500 system.

### *Statistical analysis*

The score for each criteria was compared between the control and treated group using Man Whitney summation of ranks test for nonparametric data under the value of significance ($P \leq 0.05$) by using SPSS software, version (19).

## RESULTS

The histopathological examination of the defected rat mandible sections revealed action of healing at the 7th day of experiment. Healing signs were manifested by formation of loose areolar (Figure 1) connective tissue containing unclosed gaps with remnants of hematoma formation (Figures 2,3), inflammatory cells invading multiple spots of the callus (Figure 4A), reactive zone at the periphery of the soft callus contained proliferating fibroblasts and osteoblasts from original stem cells of the compact bone (Figures 4B,4C), Gap occlusion, in Parathormone treated group on the 14th day of the experiment (Figure 4d) osteoblasts and their associated osteoid gel matrix (Figures 5A,5B) that was intensely stained with eosin at different degrees of calcification, mineralization, granulation, and purple color (Figures 5C,5D). Transformation of the mineralized osteoid matrix and their osteoblasts to form woven bone trabeculae started at some fields of the sections on the 7th day and afterward at the periphery of the callus. In the original compact bone there was evidence of bone resorption near the activated, mostly multinucleated osteoclasts (Figures 6,7). It was well noticed that differences in the intensity of these changes were present between the control and TPTD-treated groups. These were obvious by comparing the score of intensity of these changes as criteria, on the 7th day and 14th day of the experiment, with the group treated with parathyroid hormone significantly exceeded the control group in the mean ranks of each osteoblast presence, osteoid matrix density and osteoid matrix mineralization. Also the treated group was significantly superior to control group in woven bone islets formation on the 14th, 21st and 28th days of the experiment. In the original compact bone, there was bone resorption by the action and presence of the osteoclasts, which was significantly higher in the treated group than control on the 14th and 21st day of the experiment (Tables 1,2,3,4, Figure 8).

The following histological sections reveal how the scores were calculated and the differences between the control and the treated groups at the different treatment intervals:

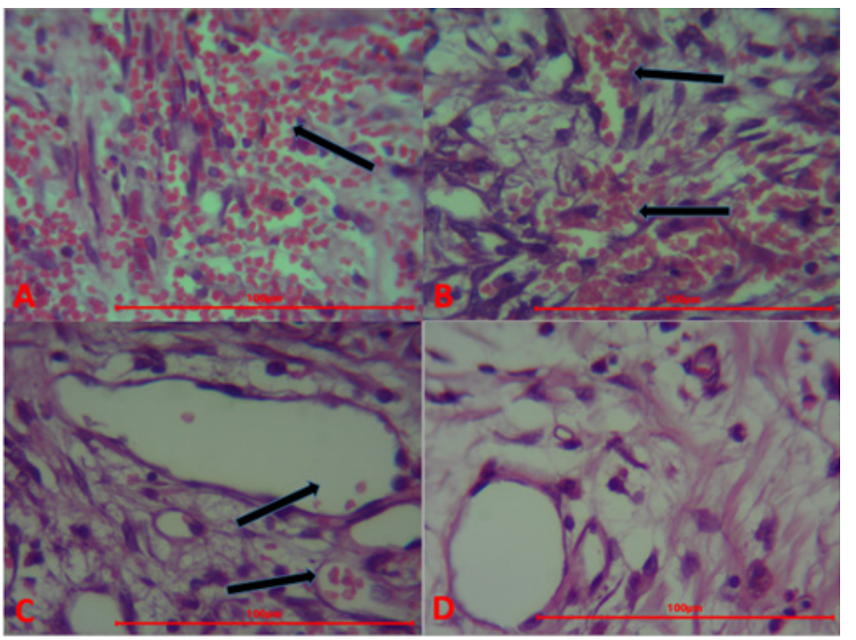


**Fig. 1:** Section in the center of the callus at the site of the defect of the rat mandible, showing variable degrees of hematoma resolution (Black arrows) at newly formed areolar connective tissue as demonstrated: **A:** Grade (0): Control group on the 7th day of the experiment. **B:** Grade (1): Parathormone treated group, 7th day of the experiment. **C:** Grade (2): Control group on the 7th day of the experiment. **D:** Grade (3): Parathormone treated group on the 7th day of the experiment. H&E stains. Scale bar 100 µm. Magnification 400 X.

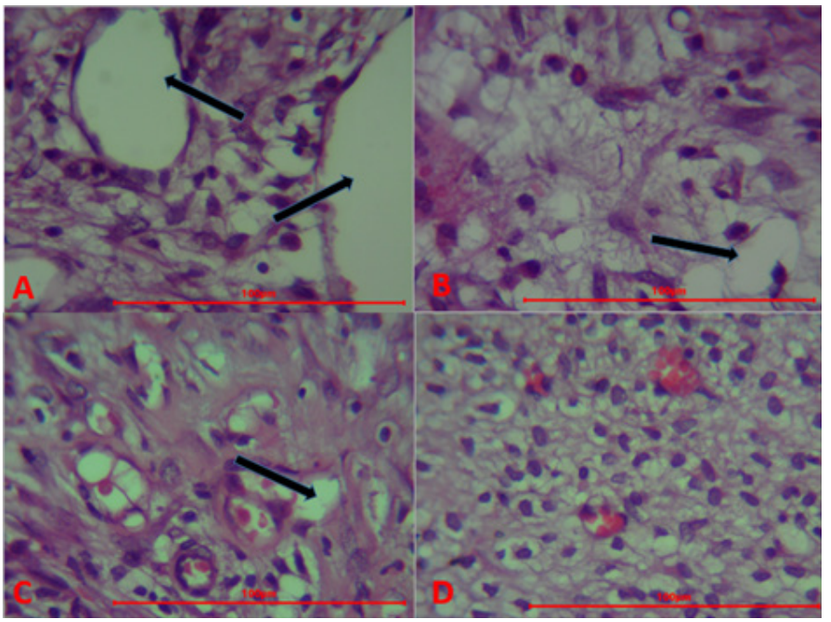


**Fig. 2:** Section in the center of the callus at the site of the defect of the rat mandible, showing variable degrees of gaps occlusion (Black arrows) at newly formed soft callus formation: **A:** Grade (0): Gap occlusion, control group on the 7th day of the experiment. **B:** Grade (1): Gap occlusion, parathormone treated group on the 7th day of the experiment. **C:** Grade (2); Gap occlusion, control group on the 28th day of the experiment. **D:** Grade (3): Gap occlusion, parathormone treated group on the 28th day of the experiment. H&E stains. Scale bar 100 µm. Magnification 400 X.

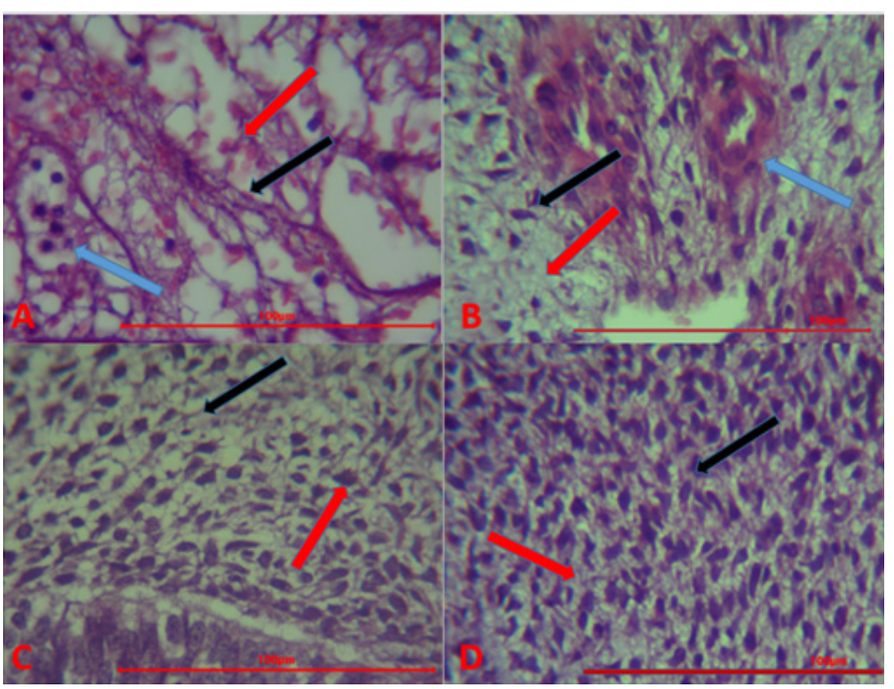


**Fig. 3:** Section in the center of the callus at the site of the defect of the rat mandible, showing variable degrees of soft callus formation demonstrated as: **A:** Grade (0): Control group on the 7th day of the experiment showing only blood remnants containing fibrin strands (Black arrow), red blood cells (Red arrow) and a few inflammatory cells (Blue arrow). **B:** Grade (1): Parathormone treated group on the 14th day of the experiment showing fibroblasts (Black arrow), collagen fibers (Red arrow) and osteoblasts surrounded by osteoid (blue arrow). **C:** Grade (2): Control group on the 21st day of the experiment revealing fibroblasts (Black arrow) and osteoblasts (Red arrow). **D:** Grade (3): Parathormone treated group on the 28th day of the experiment showing dense fibrous tissue with fibroblasts (Black arrow) and collagen fibers (Red arrow). H&E stains. Scale bar 100 µm. Magnification 400 X.

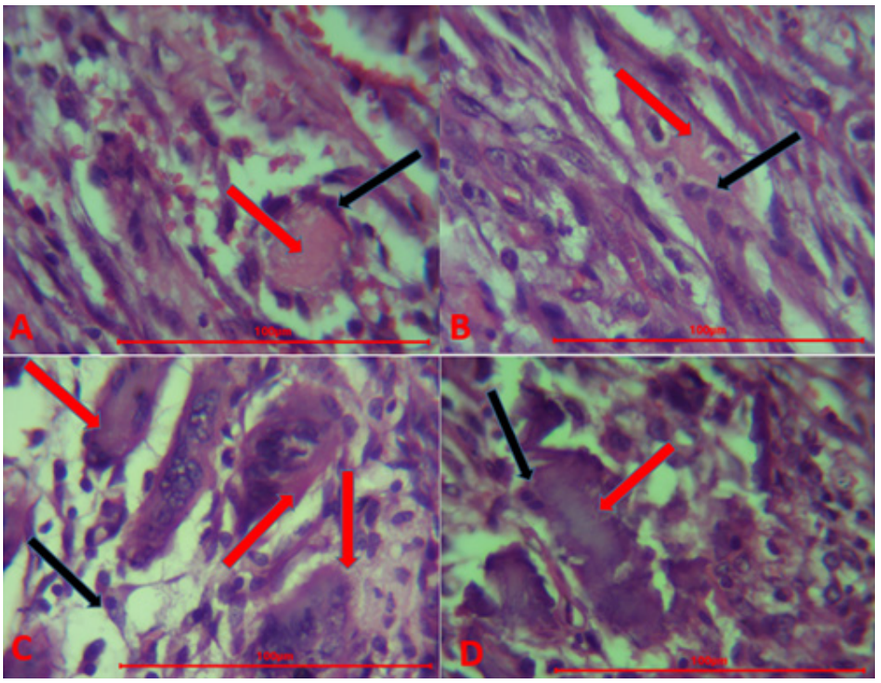


**Fig. 4:** Section in the periphery of the callus at the site of the defect of the rat mandible, showing variable degrees of osteoid islets deposition and mineralization at the microscopic fields in the soft callus with osteoid matrix (Red arrow) with different degrees of diffusion and mineralization, and presence of osteoblasts (Black arrow) which secret them: **A:** Grade (1): Control group on the 7th day of the experiment. **B:** Grade (1): Parathormone treated group on the 7th day of the experiment. **C:** Grade (2): Control group on the 14th day of the experiment. **D:** Grade (3): Parathormone treated group on the 14th day of the experiment. H&E stains. Scale bar 100 µm. Magnification 400 X.

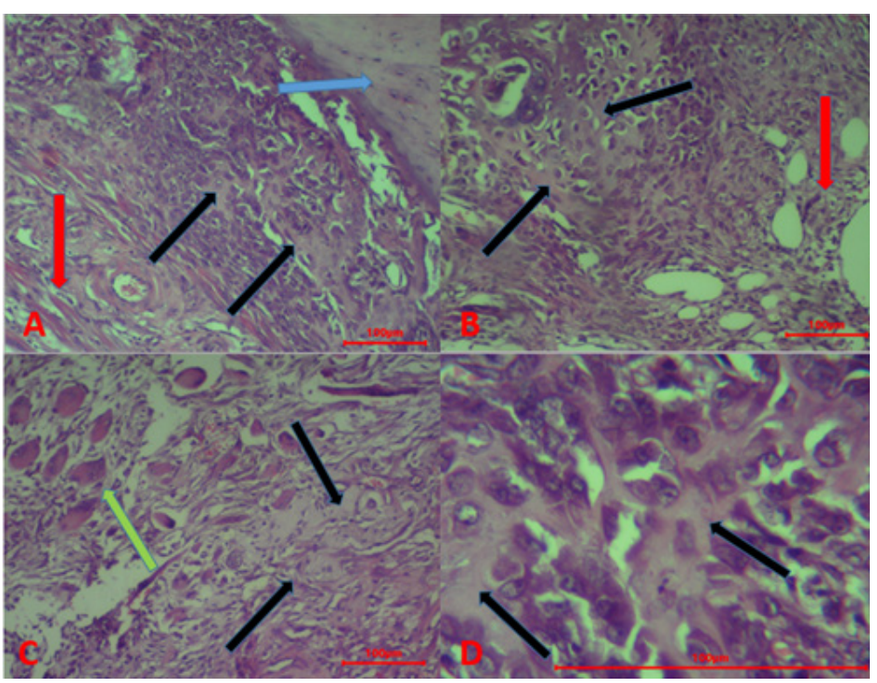


**Fig. 5:** Section in the periphery of the callus at the site of the defect of the rat mandible, showing variable degrees of forming woven bone lamellae at the microscopic fields in the periphery of the soft callus (Black arrow) with remaining of centrally located non-ossified areolar tissue (Red arrow), with the appearance of the original compact bone (Blue arrow), and osteoid matrix islets (Green arrow) at some sections:
**A:** Grade (1): Control group on the 14th day of the experiment.
**B:** Grade (2): Parathormone treated group on the 14th day of the experiment.
**C:** Grade (3): Parathormone treated group on the 21st day of the experiment.
**D:** Grade (3): Parathormone treated group on the 21st day of the experiment (Magnified view). H&E stains. Scale bar 100 µm. Magnification 100X and 400 X.

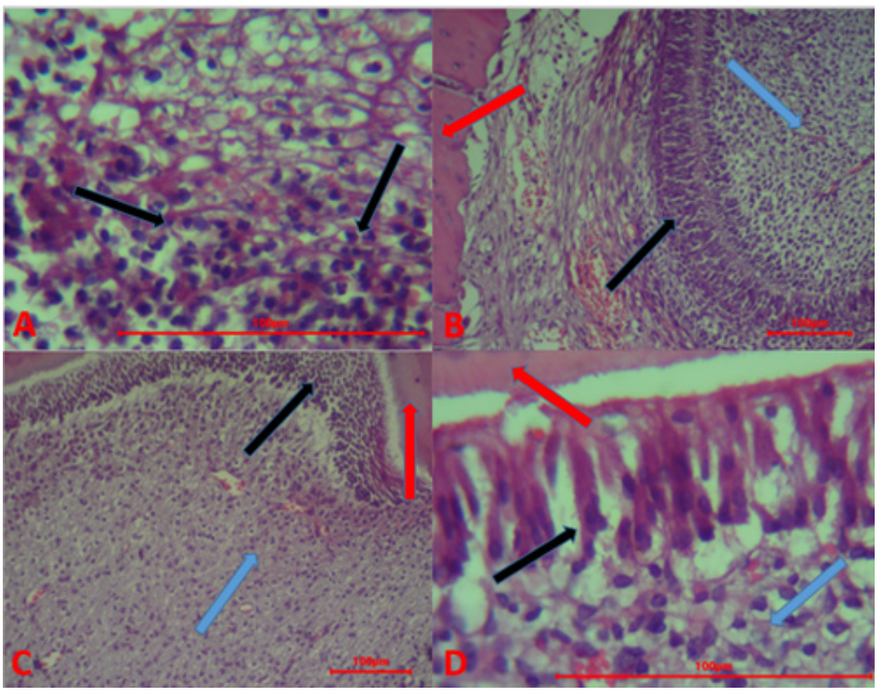


**Fig. 6:** Section in the callus at the site of the defect in the rat mandible showing: **A:** Grade (3): Control group on the 7th day of the experiment revealing large focus of inflammatory cells in the newly formed areolar tissue at the center (black arrow). **B and C** revealing the reactive zone (Black arrow) between the original compact bone (Red arrow) and non-calcified areolar tissue (Blue arrow) in the control and parathormone treated group respectively on the 14th day of the experiment. **D** represents a magnified view of C and revealing the proliferated osteoblast at the reactive zone of the callus. H&E stains. Scale bar 100 µm. Magnification 100X and 400 X.

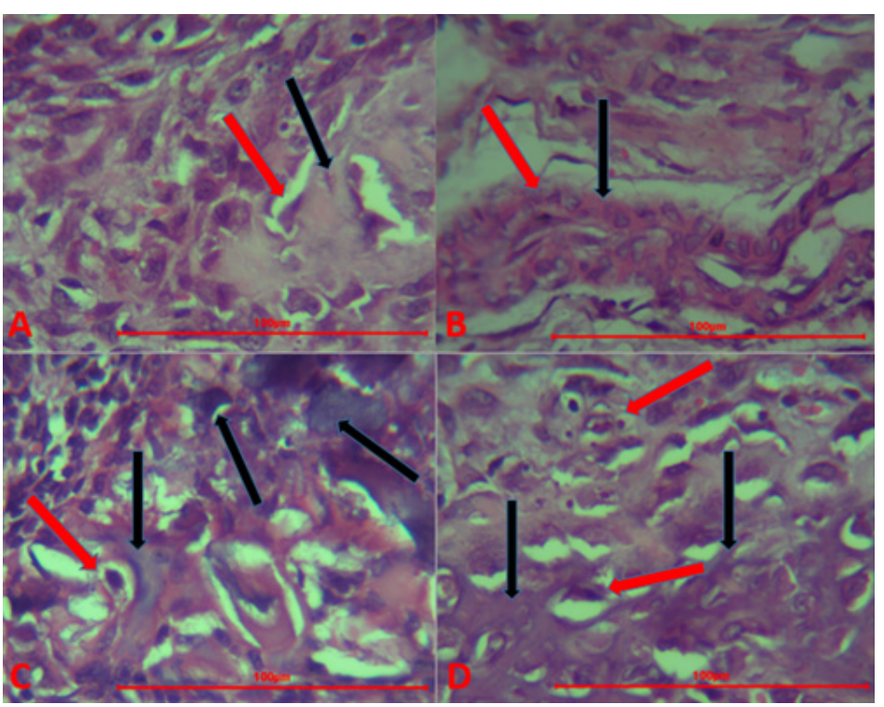


**Fig. 7:** Section in the periphery of the callus at the site of the defect of the rat mandible, showing: **A:** Woven bone lamellae (Black arrow), control group on the 14th day of the experiment. **B:** Trabecular bone plates (Black arrow), parathormone treated group on the 14th day of the experiment. **C:** Lamellar bone lacunae formation (Black arrow), parathormone treated group on the 28th day of the experiment. **D:** Initial stages of remodeling of the lamellar bone with canalization (Black arrow), parathormone treated group on the 28th day of the experiment. Osteoblasts in all images are referred to as (Red arrows). H&E stains. Scale bar 100 µm. Magnification 400 X.

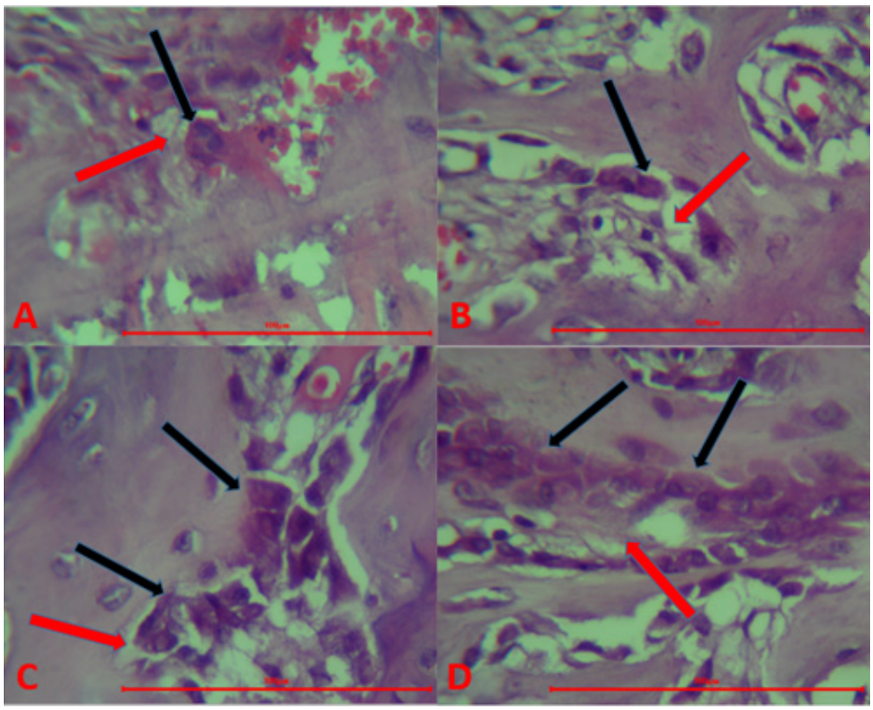


**Fig. 8:** Section in the original compact bone, at the periphery of the callus at the site of the defect of the rat mandible, showing.
**A:** Grade (1): Bone resorption manifested by multinucleated osteoclast giant cell (Black arrow) and the zone of resorption surrounding it (Red arrow), control group on the 7th day of the experiment.
**B:** Grade (1): Bone resorption manifested by osteoclast cells (Black arrow) and the zone of resorption surrounding them (Red arrow), parathormone treated group on the 7th day of the experiment.
**C:** Grade (2): Bone resorption manifested by osteoclast cells (Black arrow) and the zone of resorption surrounding them (Red arrow), control group on the 21st day of the experiment.
**D:** Grade (3): Bone resorption manifested by osteoclast cells (Black arrow) and the zone of resorption surrounding them (Red arrow), parathormone treated group on the 21st day of the experiment. H&E stains. Scale bar 100 µm. Magnification 400 X.

**Table 1:** Histological criteria of the defected area in rat mandible expressed by mean ranks and compared by Man Whitney summation of ranks on the 7th day of the experiment.

| Criteria | Control | Treatment |
|---|---|---|
| Blood cast resolution | 6.25 | 6.75 |
| Gap occlusion | 6.00 | 7.00 |
| Areolar tissue deposition | 6.00 | 7.00 |
| Osteoblast & osteoid matrix density | 3.75 | 9.25* |
| Osteoid matrix mineralization | 3.50 | 9.50* |
| Woven & trabecular bone islets | 6.00 | 7.00 |
| Inflammatory foci | 6.83 | 6.17 |
| Lamellar bone remodeling | 6.50 | 6.50 |
| Compact bone resorption & osteoclast presence | 4.00 | 9.00* |
| Lamellar bone formation | 6.50 | 6.50 |

The values manifested by the mean of ranks of the group.
*Means a significant superiority.

**Table 2:** Histological criteria of the defected area in rat mandible expressed by mean ranks and compared by Man Whitney summation of ranks on the 14th day of the experiment.

| Criteria | Control | Treatment |
|---|---|---|
| Blood cast resolution | 6.83 | 6.17 |
| Gap occlusion | 6.00 | 7.00 |
| Areolar tissue deposition | 5.33 | 7.67 |
| Osteoblast & osteoid matrix density | 4.00 | 9.00* |
| Osteoid matrix mineralization | 3.67 | 9.33* |
| Woven & trabecular bone islets | 4.33 | 8.67* |
| Inflammatory foci | 6.92 | 6.08 |
| Lamellar bone remodeling | 6.50 | 6.50 |
| Compact bone resorption & osteoclast presence | 3.67 | 9.33* |
| Lamellar bone formation | 6.50 | 6.50 |

The values manifested by the mean of ranks of the group.
*Means a significant superiority.

**Table 3:** Histological criteria of the defected area in rat mandible expressed by mean ranks and compared by Man Whitney summation of ranks on the 21st day of the experiment.

| Criteria | Control | Treatment |
|---|---|---|
| Blood cast resolution | 6.5 | 6.5 |
| Gap occlusion | 4.92 | 8.08 |
| Areolar tissue deposition | 6.00 | 7.00 |
| Osteoblast & osteoid matrix density | 5.83 | 7.17 |
| Osteoid matrix mineralization | 4.00 | 9.00* |
| Woven & trabecular bone islets | 3.75 | 9.25* |
| Inflammatory foci | 6.50 | 6.50 |
| Lamellar bone remodeling | 6.50 | 6.50 |
| Compact bone resorption & osteoclast presence | 4.25 | 8.75* |
| Lamellar bone formation | 5.75 | 7.75 |

The values manifested by the mean of ranks of the group.
*Means a significant superiority.

**Table 4:** Histological criteria of the defected area in rat mandible expressed by mean ranks and compared by Man Whitney summation of ranks on the 28th day of the experiment.

| Criteria | Control | Treatment |
|---|---|---|
| Blood cast resolution | 6.50 | 6.50 |
| Gap occlusion | 5.50 | 7.50 |
| Areolar tissue deposition | 6.50 | 6.50 |
| Osteoblast & osteoid matrix density | 6.00 | 7.00 |
| Osteoid matrix mineralization | 5.00 | 8.00 |
| Woven & trabecular bone islets | 4.50 | 8.50* |
| Inflammatory foci | 6.50 | 6.50 |
| Lamellar bone remodeling | 6.50 | 6.50 |
| Compact bone resorption & osteoclast presence | 6.50 | 6.50 |
| Lamellar bone formation | 4.25 | 8.75* |

The values manifested by the mean of ranks of the group.
*Means a significant superiority.

## DISCUSSION

Bone healing entails a complicated and overlapping set of biological processes in order to restore normal bone structure and function[1]. The physiological processes that occur at the location of the defect include inflammation, hematoma development, fibro-cartilaginous callus creation, hard callus formation, and bone remodeling. The process of bone healing is governed by a variety of components, including inflammatory, growth, and hormonal factors[10,11].

In the present study, histological analysis was used to investigate how intermittent teriparatide treatment affected the repair of a mandibular bone defect. Low-dose daily teriparatide treatment improved repair of mandibular defects at both early and late postoperative time points. Histological evaluations of the healing defect site for the teriparatide-treated group on postoperative days 7, 14, 21 and 28 revealed enhanced bone healing in the form of greater amounts of osteoblasts, osteoid matrix density, osteoid matrix mineralization, areolar tissue deposition, woven and trabecular bone islets and gap occlusion.

The findings of the current study agreed with several animal studies. In a rat model study carried by (Rowshan *et al*. 2010)[12], the effect of 10 µg/kg/day teriparatide on the healing of mandibular fractures, stabilized with an external fixation device, was evaluated, and enhanced healing of mandibular fractures was observed. In another study by (Zandi *et al*. 2019)[24] to evaluate the impact of short-term teriparatide on the healing process of autologous bone grafts in mandibular critical-size defects in rats. A dose of 2 µg/kg/day was administered for 20 days, and the results revealed that bone defects in teriparatide-treated rats had more new bone formation and bone maturation and shorter healing time compared to those in the control rats.

In a study for histological assessment of the effects of teriparatide therapy on mandibular fracture healing in rats by (Zandi *et al*. 2020)[13], a dose of 2 µg/kg/day of teriparatide subcutaneously was used for 30 days. The results showed the presence of greater amounts of woven bone and less fibrous tissue for the teriparatide group in the earlier stages, with promotion of remodeling of trabecular to mature bone in the later stages of the healing process.

In the current study, the group treated with teriparatide significantly exceeded the control group in the mean ranks of each osteoblast presence, osteoid matrix density and osteoid matrix mineralization on the 7th day and 14th day of the experiment. Also the treated group was significantly superior to the control group in woven bone islets formation on the 14th, 21st and 28th days of the experiment. In the original compact bone, there was bone resorption by the action and presence of the osteoclasts, which was significantly higher in the treated group than the control group on the 14th and 21st day of the experiment.

Teriparatide, an FDA-approved therapeutic agent for osteoporosis, is a synthetic variant of the first 34 amino-terminal residues of human parathyroid hormone. Due to its well-recognized anabolic properties, this substance has been regarded as a promising option for systemic administration in order to facilitate the process of bone regeneration[14]. In cases of prolonged exposure to parathyroid hormone (PTH), such as in individuals with hyperparathyroidism, bone resorption exceeds bone production. Conversely, intermittent exposure to low doses of PTH, as shown with the daily injection of teriparatide, stimulates bone growth to a greater extent than bone resorption[15]. Teriparatide is a synthetic derivative of parathyroid hormone (PTH) that specifically interacts with PTH type 1 receptors (PTH type 1R) through its N-terminal component[16]. PTH type 1R refers to a family of G-protein coupled receptors (GPCR) that are found on the surfaces of many types of cells. These receptors play a crucial role in the physiological effects of PTH on calcium and phosphate regulation, as well as bone metabolism. The primary cell types expressing PTH type 1R in relation to these traditional physiological functions are osteoblasts, osteocytes, and renal tubular cells[17].

The anabolic effects of intermittent parathyroid hormone (PTH) are facilitated by (1) the upregulation of

transcriptional expression of pro-osteoblastogenic growth factors, such as insulin-like growth factor 1 (IGF1) and fibroblast growth factor 2 (FGF2), (2) affecting the Wnt/beta-catenin osteoanabolic signaling pathway by decreasing the production of sclerostin, which is a Wnt antagonist, and (3) increased Runx2 expression and activity; Runx2 is a transcription factor critical for osteoblast differentiation[18]. PTH receptors are found on osteoblasts, which are cells that make new bone, but not on osteoclasts. In addition, giving PTH in an intermittent way has an anabolic effect on bone[19]. The precise mechanism behind the observed increase in bone formation is still not fully understood. However, it is hypothesized as a combination of mechanisms, including enhanced osteoblastogenesis, decreased osteoblast cell death (apoptosis), and the activation of various growth factors and cytokines within the local bone marrow microenvironment. Notably, the involvement of insulin-like growth factor 1 (IGF-1) and transforming growth factor beta (TGF-b) has been implicated in this process[20]. PTH is also believed to induce the mobilization of pre-osteoblasts from the stromal cells in the bone marrow[21]. The regulation of osteoblast progenitors is governed by local signaling pathways, including Wnt/beta-catenin signaling, Indian Hedgehog (IHH), and bone morphogenic protein (BMP). The Wnt/b-catenin signaling system specifically enhances the differentiation, activity, and survival of osteoblasts, but its effects are counteracted by the presence of sclerostin[22]. Previous studies have shown that parathyroid hormone (PTH) has the ability to decrease the levels of sclerostin protein in both mice and rats, leading to an augmentation of Wnt signaling, an increase in osteoblast populations, and ultimately an elevation in bone mass. The administration of teriparatide (TPTD) has been shown to result in a decrease in sclerostin levels in human subjects[23]. Teriparatide therapy improves bone healing owing to its effect on osteoblasts and osteoclasts, callus formation and bone remodeling which finally lead to the restoration of form and function of the defected bone. The outcomes are derived from the coordinated activities of osteoclasts and osteoblasts[13].

The effects of parathyroid hormone (PTH) on cortical and cancellous bone exhibit different variations. The anabolic action of this substance is more pronounced in cancellous bone than in cortical bone[24]. The low dosage of 10µg/kg/day was selected in order to prevent the potential adverse effects associated with high-dose administration of the drug. Additionally, this dosage was chosen due to its similarity to the established therapeutic dose used for the treatment of osteoporosis. Moreover,[25] demonstrated that dosages as low as (10µg/kg/day) in a rat fracture model increased both mechanical strength and bone mass of callus formation in a rat femur fracture model.

There were a number of limitations to this study. Primarily, the experiment was conducted on an animal model, which has a different physiology, drug metabolism, bone turnover, and likely bone repair process than humans. Second, no comparison was made between the effects of different dosages and durations of teriparatide treatment on bone healing; only the effects of a single dose (10 µg/kg/day) were studied. Third, the effects of teriparatide on bone healing over a longer period (more than 2 months) were not studied. Therefore, more studies on the long-term benefits of teriparatide treatment on bone defect repair are strongly encouraged, as are more investigations employing big animals and clinical trial research.

## CONCLUSION

The current study provided evidence that the regular administration of a low dosage of teriparatide over a span of 28 days resulted in improved and accelerated repair of mandibular critical-size abnormalities in rats. The rats that received teriparatide treatment exhibited enhanced bone production and maturation, as well as a reduced healing time, in comparison to the control rats, with respect to bone defects.

## ACKNOWLEDGMENT

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## CONFLICT OF INTERESTS

There are no conflicts of interest.

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**الملخص العربى**

# التقييم النسيجي لتاثيرعلاج تيريباراتيد على شفاء عيب عظم الفك السفلي في الجرذان

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**خلفية الدراسة:** بعد الإصابات أو الالتهابات أو إزالة الورم، تكون إعادة بناء العظام ضرورية للشفاء الداخلي. من بين الطرق العديدة المستحثة لإصلاح عيوب العظام هي تقنية الغشاء، والخيفي، والاصطناعي، والذاتي. ومع ذلك، فإن الزرع الجراحي لطعم العظام ومواد حشو العظام في موقع عيب العظام قد يسبب الوذمة والعدوى ونمو العظام غير المتجانسة. ولذلك، فإن الأدوية الجهازية العظمية ستكون علاجًا متميزًا لآفات العظام.

**الهدف من الدراسة:** تقييم التأثير الجهازي للتيريباراتيد على شفاء العظام بعد الحث الجراحي للعيوب العظمية في الفك السفلي لدى الفئران.

**المواد والطرق:** في هذه الدراسة، تم فصل ٤٠ فأراً ألبينو إلى مجموعتين (مجموعة السيطرة ومجموعة العلاج) تضم كل منهما ٢٠ فأراً. تم إجراء نفس الإجراء الجراحي على جميع الفئران. تم عمل ثقب في الفك السفلي (قطره ٣ مم وعمقه ٣ مم) وتركه فارغًا. تم إعطاء تيريباراتيد بجرعة (١٠ ميكروجرام/كجم) حقناً تحت الجلد يومياً للمجموعة المعالجة. تم الموت الرحيم للحيوانات على أربع فترات زمنية (٧، ١٤، ٢١ و ٢٨) يومآ. تم فصل الفك السفلي، وحفظه، وإرساله للتحليل النسيجي.

**النتائج:** كشفت النتائج أن هناك زيادة في تكوين العظام الجديدة ووقت شفاء أقصر في المجموعة المعالجة بالتريباراتيد. في اليوم السابع واليوم الرابع عشر من التجربة تفوقت المجموعة المعالجة بهرمون الغدة الجار درقية معنوياً على المجموعة الضابطة في متوسط الرتب لكل من وجود الخلايا العظمية وكثافة المادة العظمية وتمعدن المادة العظمية كما تفوقت المجموعة المعالجة معنوياً على المجموعة الضابطة في تكوين الجزر العظمية المنسوجة في الأيام ١٤ و ٢١ و ٢٨ من التجربة.

**الخلاصة:** أظهرت الفئران التي عولجت بالتيريباراتيد إنتاجًا ونضجًا محسنًا للعظام، بالإضافة إلى انخفاض وقت الشفاء اذا ماتمت مقارنتها بفئران التحكم، فيما يتعلق بعيوب العظام.