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The effect of teriparatide on fracture union in rats with chronic kidney disease

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This study aims to examine the effect of teriparatide on fracture healing in a rat model with chronic kidney disease (CKD).

A total of 32 adult, male Sprague-Dawley rats were randomly assigned to four groups: Group I (control group, teriparatide -), Group II (CKD +, teriparatide -), Group III (control group, teriparatide +) and Group IV (CKD +, teriparatide +) (n=8 each). To create CKD model, 5/6 nephrectomy was performed in the CKD groups. A proof of CKD in the CKD model was ascertained through BUN and creatinine levels in blood samples. Osteotomy of the femur was performed on all rats at the same time. Fractures were fixed using a K-wire. Eight rats from the control group (Group III) and 8 rats from the CKD group (Group IV) received a daily doses of 20 µg/kg/day teriparatide. Plain radiographic imaging was performed at 4th week. Rats were then sacrificed at the 8th week, and right femurs were removed for histological evaluation. For radiographical analysis, outcome measures such as Allen scoring, callus thickness, and Rust scoring were obtained.

The results of radiological analysis showed that teriparatide had no effect on the callus thickness of the control group, while the callus thickness was the least in Group II (p=0.041). There was no significant difference in the pathological fusion analysis between the groups.

While teriparatide has been shown to increase callus thickness, it does not exert a significant influence on the process of fracture union, neither enhancing nor inhibiting it.

INTRODUCTION

The kidney plays a significant role in bone development and has a very complicated relationship with bones[1]. Kidneys also have indirect effects on parathormone (PTH) release and direct effects on calcium absorption, phosphate absorption, and vitamin D production. Increased PTH and metabolic changes in chronic kidney disease cause osteoporosis, increased bone fragility, and problems in fracture healing[2,3].

PTH is a “key systemic regulator” for calcium and phosphate[4]. Teriparatide (PTH [1–34]) is the N-terminal peptide of the parent hormone PTH, which is in charge of serum calcium homeostasis[5]. Teriparatide was first used in treatments for osteoporosis in women and for bone loss inhibition in men6. Intermittent administration of PTH analogs has been found to provide an anabolic impact on bones by enhancing bone mass and decreasing bone loss that paves the way for enrichment of bone formation[7–11]. Recombinant PTH analogs used in the treatment of osteoporosis have positive effects on fracture union[12,13]. On the other hand, some clinical studies have found no effects on pain and fracture union[14].

Numerous scholarly inquiries within the literature have investigated the impact of teriparatide on the prevention of osteoporosis and the preservation of bone mineral equilibrium in CKD cohorts. Our research endeavors to elucidate the potential benefits of teriparatide administration in facilitating union among CKD afflicted with fractures.

MATERIALS AND METHODS

This experimental study was conducted at Başkent University, Faculty of Medicine, Department of

Orthopaedic Surgery and Traumatology between May 2018 and July 2018. The project numbered DA 18/07 was approved by the decision of the Başkent University Medical and Health Sciences Research Board and Animal Experiments Ethics Committee on 19/02/2018 (No. 18/05). All experimental procedures were carried out in accordance with the principles of Guide for the Care and Use of Laboratory Animals proposed by the National Institute of Health.

In this study, the sample size was determined to achieve a statistical power of 80% with a significance level of 0.05. A total of 32 adult, male Sprague-Dawley rats were randomly assigned to four groups: Group I (control group, teriparatide -), Group II (CKD +, teriparatide -), Group III (control group, teriparatide +) and Group IV (CKD +, teriparatide +) (n=8 each). All rats were kept under climate-controlled conditions, i.e., 18 to 20°C, 55% humidity, alternating 12 hours of light and 12 hours of darkness, and were fed with a standard diet. At the conclusion of the experiment, all rats were sacrificed by cervical dislocation under general anesthesia, in accordance with institutional animal care and use guidelines and the ARRIVE recommendations.

Previous studies have demonstrated the effects of teriparatide administration at varying doses and frequencies (10-60 µg/kg/day or week) on fracture healing[15–17]. In the present study, teriparatide (rPTH; Forsteo®, Eli Lilly and Co., Indianapolis, IN, USA) was administered subcutaneously to the CKD groups at a dose of 20 µg/kg/day once daily, in accordance with previously established experimental protocols.

Surgical procedure for nephrectomy

Chronic kidney disease was induced in the animals by a one-step modified 5/6 nephrectomy procedure as prescribed in the literature18. Briefly, the right renal hilum was exposed and tied with a 5-0 Vicryl suture proximal to the kidney using a small flank incision. While maintaining hemostasis, the kidney was taken. After the removal, the left kidney was exposed to the same procedure. Yet, the renal pedicle was clamped shortly with subsequent electrical cauterization of 50 to 75% of the renal cortex after the clearance of the renal capsule in order that at least 1-mm around the hilum remained non-injured. Special attention was given not to disturb the ureters. Incisions were closed using a standard two-layer technique consisting of the closure of the peritoneum and body wall muscle with a 4-0 Vicryl suture, and then, skin approximation with 4-0 silk sutures. Nephrectomy day was accepted as Day 0.

Serum biochemical assays

Four weeks later than renal surgery, blood samples were obtained by cheek pouch puncture. Serum biochemistry was performed with commercially available kits including blood urea nitrogen (BUN), creatinine, and hemoglobin levels (Roche Diagnostics, IN, USA) according to the manufacturer's instructions. Blood values of the CKD groups were measured on Day 0 and at four and eight weeks.

Osteotomy and fixation surgeries

Following the formation of CKD at four weeks, the rats were subjected to osteotomy in the right femurs. First, transverse femoral shaft fracture was performed in the right femur using a high-speed burr. To prevent thermal necrosis and infection during surgery, the surgical area was continuously irrigated with saline solution. Then, a 1.2-mm diameter K-wire was put into the right femoral intramedullary canal in a retrograde fashion[19].

Histological evaluation

At eight weeks, after sacrifying animals, their fractured femur was removed and was, then, fixed in 4% paraformaldehyde, decalcified, and embedded in paraffin wax. Sagittal sections were made ready and stained with hematoxylin-eosin. The Allen score using a seven-point scale (from 0 to 6) for evaluating fracture healing was applied by four orthopedic surgeons who were blinded to the groups[20]. The grades represented the healing status as grade 0, nonunion; grade 1, incomplete cartilaginous union (fibrous elements); grade 2, complete cartilaginous union; grade 3, incomplete bony union (small amount of cartilage present in callus); grade 4, incomplete bone union (equal amount of cartilage and bone elements); grade 5, incomplete bone union (small amount of cartilage elements with high amount of trabecular bone); and grade 6, completed bone tissue. Additionally, the presence of necrosis was assessed (Figure 1).

Radiological evaluation

At four weeks, fractured limb radiographs from anteroposterior (AP) and lateral views were obtained. Callus thickness was defined as the distance between the cortical bone healing site and the outermost margin of the callus. Each callus, on the four cortices (2 from AP and 2 from lateral views), was evaluated by four senior orthopaedic surgeons. A bony union was determined when three of the four cortices were linked and/or when the fracture lines vanished totally[21,22]. Besides, a non-union status was given,

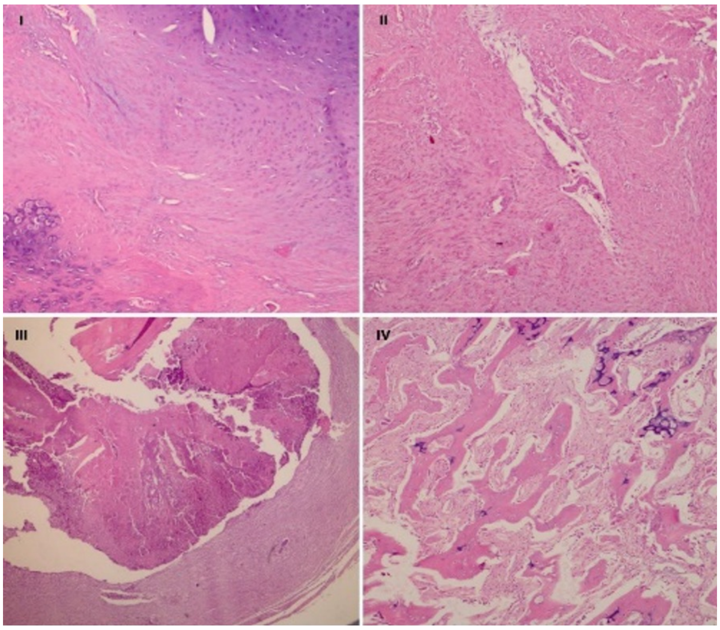

Fig. 1 — Histological evaluation of fracture union. I) Allen score 3 in CKD(-) teriparatide(-) group; II) Allen score 1 in CKD(+) teriparatide(-) group; III) Allen score 0 in CKD(-) teriparatide(+) group; and IV)Allen score 5 in CKD(+) teriparatide(+) group. CKD: chronic kidney disease.

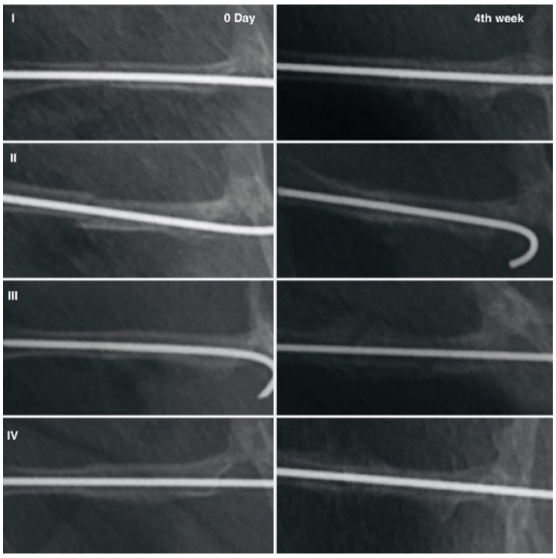

Fig. 2 — Radiological evaluation of fracture union. I) Right femur of CKD(-) teriparatide(-) group showing Day 0 and Week 4; II) Right femur of CKD(-) teriparatide(-) group showing Day 0 and Week 4; III) Right femur of CKD(-) teriparatide(-) group rat showing Day 0 and Week 4; and IV) Right femur of CKD(-) teriparatide(-) group rat showing Day 0 and Week 4. CKD: chronic kidney disease.

when none of the sides of the callus was connected in these views[21]. Initially developed for assessing fracture healing in human tibial fractures, the RUST scoring system has proven to be a reliable tool for evaluating human femoral fractures and long bone union in animal models as well. Tawonsawatruk et al. reported excellent interobserver and intraobserver reliability of the RUST score when applied in experimental animal studies[23,24]. The RUST scores were also calculated (Figure 2).

RESULTS

Biochemical Evaluation

Results obtained from all rats at day 1 and weeks 4 and 8 are presented in Table I. In the CKD Groups II and IV BUN values increased by 2.7 times in the 4th week and 2.9 times in the 8th week. The value of creatin rose 1.7 times in the 4th week and 1.9 times in the 8th week in the same groups. The weight of rats in the control groups did not change in the 4th week, while a decrease of 6% was observed in the 8th week. In the CKD group, a 25% decrease in weight was observed in the 4th week and 21% in the 8th week (Table I).

Histological and Radiological Evaluation

Allen scores was 3.38±1.302 in Group I, 3.88±1.458 in Group II, 2.5±1.604 in Group III, 3±1.927 in Group IV (Table II). RUST scores was 2.38±0.518 in Group I, 2±0.756 in Group II, 2.25±0.463 in Group III, 2.75±0.463 in Group IV. Callus thickness was 1.538±0.7763 in Group I, 0.738±0.6781 in Group II, 1.775±0.7126 in Group III, 1.5±0.3464 in Group IV (Table III).

In histological and radiological evaluations, no statistically significant difference was detected between the groups, except for callus thickness. Callus thickness was statistically significantly lower in Group II. ($p=0.041$) Throughout the experimental period, no mortality related to CKD was observed among the subjects.

DISCUSSION

Abnormal mineral metabolism in CKD, referred to as CKD-associated mineral and bone disorder (CKD-MBD), negatively affects bone fragility and healing[2,3,25,26]. In this study, which we conducted to investigate the effect of teriparatide used in CKD patients on fracture healing, we evaluated the BUN, Cre increase and Hgb decrease to evaluate

Table I. — Biochemical parameters and body weights of control and CKD rats.

Control (Group I -III)				CKD (Group II-IV)		
	Day 0	W 4	W 8	Day 0	W 4	W 8
Hemoglobin (g/dL)	15.1	14.7	14.5	15.06	12.75	12.4
BUN (mg/dL)	17	16.8	17.3	17.5	47.3	51.25
Creatinine (mg/dL)	0.42	0.41	0.44	0.43	0.75	0.8
Weight (g)	410	407	385	420	330	317

CKD: chronic kidney disease; W: week; BUN: blood urea nitrogen.

Table II. — Histological results of control and CKD rats (right femurs).

Histological Results			
Group	Allen scores	Vascular proliferation	Inflammation
I (CKD- rPTH-)	3.38±1.302	0.5±0.535	0.63±0.518
II (CKD+ rPTH-)	3.88±1.458	0.63±0.518	0.88±0.354
III (CKD- rPTH +)	2.5±1.604	0.5±0.535	0.88±0.354
IV (CKD+ rPTH+)	3±1.927	0±0	0.5±0.535

Data are given in mean ± standard deviation, unless otherwise stated. CKD: chronic kidney disease; rPTH: recombinant parathyroid hormone.

Table III. — Radiological results of control and CKD rats (right femurs).

Radiological Results			
Group	Connection	RUST scores	Callus thickness mm
I (CKD- rPTH-)	0.63±0.518	2.38±0.518	1.538±0.7763
II (CKD+ rPTH-)	0.25±0.463	2±0.756	0.738±0.6781
III (CKD- rPTH +)	0.25±0.463	2.25±0.463	1.775±0.7126
IV (CKD+ rPTH+)	0.75±0.463	2.75±0.463	1.5±0.3464

Data are given in mean ± standard deviation, unless otherwise stated. CKD: chronic kidney disease; rPTH: recombinant parathyroid hormone.

the occurrence of CKD. In CKD groups, BUN levels increased 2.7 times in the 4th week and 2.9 times in the 8th week, and serum creatinine levels in the same groups increased 1.7 times in the 4th week and 1.9 times in the 8th week. It was observed that it was compatible with the CKD model created by Gagnon et al[27].

Zhang et al. studied different doses of recombinant PTH 1-34 activity by forming a fracture model in the tibia of rats. Dual-energy X-ray absorptiometry, micro-CT, three-point bending biomechanics test, and histology in the 4th week showed the positive effect of 20 µg/week teriparatide on bone union equivalent to 10 µg/day teriparatide application[17]. Nishitani et al. researched allograft and plate screw fixation by forming a 5 cm defect in the femoral diaphysis of Mongrel hound dogs. In comparison with the control group, the intermittent high-dose rPTH1-34 group showed an increase in mineral opposition in callus formation in 8 weeks ($p < 0.005$). They also showed that callus formation was larger in the rPTH groups; but there was no biomechanical difference.

Previous studies have demonstrated the positive effects of teriparatide on fracture healing under various conditions that impair bone repair. Zandi et al. showed histological improvement in mandibular fractures, Oz et al. reported enhanced healing in osteoporotic femoral fractures, and Kanezaki et al. demonstrated similar benefits in an open femoral fracture model[28–30]. In our study, the fracture model was applied in the right femur bones of rats. They were given 20 µg/day teriparatide and histological and X-ray evaluation were performed. Histological evaluation showed that teriparatide had no effect on fracture union in both healthy rats and CKD rats, but callus thickness was statistically significantly lower in group 2 ($p=0.041$). Callus thickness of group 4 was similar to the healthy groups, we interpreted this as an effect of teriparatide. However, micro-CT and biomechanical tests were not performed in this study.

Other studies have investigated the potential impact mechanism of PTH in fracture healing[31,32]. PTH (1-34) has two possible mechanisms on fracture healing: stimulating the differentiation of osteoblasts or endochondral bone formation and differentiation acceleration by promoting chondrocyte proliferation[33,34]. Nakajima et al. demonstrated that PTH (1-34) enhances fracture healing by promoting the proliferation of osteoblastic progenitor cells, synthesis of bone matrix proteins, and stimulation of osteoclastogenesis, thereby improving both callus formation and callus remodeling in a rat closed femur fracture model[33]. Nakazawa et al. showed that PTH treatment helped the recruitment of mesenchymal cells into the chondrocyte lineage and increased the proliferation of chondroprogenitor cells, thus forming a callus formation with a larger cartilage structure in the same fracture model[34]. In our study, callus thickness in Group IV, which teriparatide was used, was larger than in Group II. Our interpretation in our study is consistent with aforementioned studies.

Following the formation of femur atrophic nonunion in 32 rats, Kumabe et al. administered rPTH to half of the rats. Allen scores were significantly higher in the PTH group compared to the control group according to histological assessment for the repair rate ($p<0.05$). Again, ultimate stress and stiffness values were also significantly greater in the PTH group ($p< 0.05$) at the end of the 8th week[35]. There is no statistically significant difference in our study according to Allen scores.

Many studies on the dose of PTH1-34 used in fracture healing can be found in the literature. Several of them have reported that PTH 1-34 has a positive effect on fracture healing when given 3 times a week[36–38]. Komatsubara et al. showed that the use of PTH1-34 once every 3 weeks contributed to the union in a fracture model created by osteotomy[37]. Nishitani reported positive results in dogs with a dose of 5 µg/kg/day for 8 weeks12. On the other hand, clinical case reports have reported that PTH 1-34 increases union in fractures with non-union and late-union symptoms[39,40]. In our study, no significant effect on fracture union was observed.

Similar studies have used micro-CT to radiologically evaluate the union and 3-point bending test for biomechanical evaluation[12,17]. In the current study however, only X-ray images were used for radiological evaluation, which can be considered a limitation. Micro-CT is a more successful method in the evaluation of trabecular and cortical bone architecture in rats compared to conventional radiological methods. In addition, the lack of biomechanical evaluation in this study was a major deficiency as well. We did not want to increase the number of animals used in the experiment, so we didn't perform biomechanical assessment. The number of limbs evaluated can be doubled through the use of biomechanical evaluation or by performing simultaneous osteotomy in both femurs of rats. However, this option was not utilized to prevent pain in rats and severely restricted movement.

CONCLUSION

While teriparatide has been shown to increase callus thickness, it does not exert a significant influence on the process of fracture union, neither enhancing nor inhibiting it.

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