

## Intermittent Parathyroid Hormone Injection Can Decrease Femoral Head Collapse in the Vascular Deprivation of Rat Femoral Head Model

### Abstract

**Backgrounds:** Intermittent parathyroid hormone (intermittent PTH) injection has been shown to improve osteogenesis. We hypothesized that intermittent PTH injection could stimulate osteogenesis during the early phase of vascular deprivation-induced femoral neck osteonecrosis in a rat model. **Materials and Methods:** Eighteen Sprague-Dawley rats were divided into three groups (normal saline [CON], PTH 10 µg/kg [PTH-H], and PTH 1 µg/kg [PTH-L]) for 8 weeks by subcutaneous injection. All rats were sacrificed at postoperative 8 weeks, and all underwent a micro-computed tomography (µ-CT) examination for bone quality and quantity evaluation and histomorphometric analysis for microscopic histologic differences. **Results:** Under µ-CT examination, both the PTH-H and PTH-L groups revealed less bone resorption than the control group. The PTH-H group had a better bone protective effect than the PTH-L group. Bone mineral density was increased in the PTH-H and PTH-L groups compared to the control group. The uninjured left femoral head was enlarged in both PTH groups. The histologic examination showed that both PTH groups had new bone and cartilage formation. The control group had only dead bone without any osteogenesis. **Conclusion:** Intermittent PTH injection could decrease bone resorption and improve bone density, compared to the control group, in vascular deprivation of the femoral head in a rat model. High-level intermittent PTH injection had a better effect than low-level intermittent PTH injection.

**Keywords:** *Avascular necrosis, Micro-computed tomography, Parathyroid hormone*

### Introduction

Osteonecrosis of the femoral head (ONFH) can result in bony structure deformity and osteoarthritis of the hip joint. Several pathologic conditions, such as trauma, steroid intake, hemostatic disease, and Caisson's disease, may result in ONFH.<sup>1</sup> In the early stage of ONFH, a joint-preserving procedure could be the first choice of treatment but with an uncertain success rate.<sup>2</sup> Total hip arthroplasty is the "gold standard" of treatment for ONFH with severe articular destruction.<sup>3</sup> Although total hip arthroplasty has a high patient satisfaction rate, recent studies have revealed that young patients have a lower satisfaction rate due to the longevity limitation of hip arthroplasty.<sup>4</sup>

Nowadays, the risk factors for ONFH have been studied well, but the true pathogenesis that results in the collapse of the femoral head is still unclear. Osteocyte death along with bone canaliculi does not result in femoral head collapse. Several studies revealed that alteration

of the femoral head bony structure in the ONFH patient was due to an imbalance of the bone resorption and repair process.<sup>5</sup> Excess osteoclast bone resorption activity would offset osteoblast bone repair activity in the ONFH patient.<sup>6</sup> The femoral head would lose mechanical strength with the progressive bone resorption process and finally collapse.

Parathyroid hormone (PTH), consisting of 84 amino acids, plays a critical role in maintaining calcium balance and bone metabolism. Different ways of administration of PTH would result in either an anabolic or catabolic effect on the skeletal system.<sup>7</sup> Continuous administration of PTH results in liberating calcium from the skeleton by increasing osteoclast activity. In contrast, intermittent administration of PTH would result in an anabolic effect by promoting osteoblast maturation and differentiation and inhibiting osteoblast apoptosis.<sup>8,9</sup> The anabolic effect of PTH has been proven to increase bone mineral density (BMD) and improve fracture healing.<sup>10-12</sup>

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DOI:  
10.4103/ortho.IJOrtho\_315\_17

### Quick Response Code:



**How to cite this article:** Chiang CW, Chen WC, Lee CH, Chen CH. Intermittent parathyroid hormone injection can decrease femoral head collapse in the vascular deprivation of rat femoral head model. *Indian J Orthop* 2019;53:340-6.

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In this study, we hypothesized that intermittent PTH injection would decrease femoral head collapse in ONFH of a rat model based on the anabolic effect. We used micro-computed tomography ( $\mu$ -CT) to evaluate the extent of femoral head collapse and BMD. We also used histology to evaluate new bone formation and necrotic bone resorption at the microscopic level.

## Materials and Methods

### Surgical procedures for an osteonecrosis model of rats

All animal procedures were carried out according to the Guide for the Care and Use of Laboratory Animals and were approved by the Committee of Experimental Animal Sciences of our institute. Blood circulation in the right femoral head of 18 Sprague-Dawley rats (weighing around 400 grams) was interrupted to create a surgical model of ONFH.<sup>1</sup> The rats were anesthetized with an intramuscular injection of ketamine (120 mg/kg, Sigma, St. Louis, MO) and xylazine (17 mg/kg, Bayer, Kyonggi-do, Korea). The longitudinal incision at the greater trochanter was made on shaved, antiseptic clean skin. The gluteus maximus muscle was split, and two-thirds of the gluteus medius muscles were detached by knife. The right hip capsule was transected along the trochanteric ridge. Then, the femoral head was dislocated totally by cutting the ligamentum teres. The femoral head was relocated and the gluteal muscles were sutured after checking that the entire capsule was incised.

### Evaluation of intermittent parathyroid hormone injection

To evaluate PTH (Lilly France, Fegersheim, France), the study animals were divided into three groups, a control group (normal saline, CON), a PTH high-dose group (10  $\mu$ g/kg, PTH-H), and a PTH low-dose group (1  $\mu$ g/kg, PTH-L); each group consisted of six rats. All rats underwent subcutaneous injection (0.1 ml/0.1 kg) every day for 8 weeks, respectively, in accordance with their PTH dose groups. All rats were sacrificed by CO<sub>2</sub> inhalation 8 weeks postoperatively, and both sides of the femoral heads were harvested for  $\mu$ -CT and histologic examination.

### Examination of micro-computed tomography

The femur samples were fixed and prepared for further scanning by  $\mu$ -CT. Bruker Skyscan 1176 (Skyscan, Kontich, Belgium) was used to scan samples with  $9 \times 9 \times 9 \mu\text{m}^3$  voxel size. Scanning was done at 65 keV of voltage, 380  $\mu$ A of current, 985 ms of exposure time, and with a 1 mm aluminum filter. Reconstruction of sections was carried out with GPU-based scanner software (NRecon). The grayscale was based on the Hounsfield unit, and the validated calcium standards were scanned as its density reference. CTAn (Skyscan) was used to analyze the epiphysis area where can be identified refer to the growth plate. The region of interest was analyzed and the binary

density (85 to 255) was considered as positive in this study. The three-dimensional (3D) morphometric indices and BMD of the target volume were then calculated by CTAn software. For illustration, CTVox (version 2.7, Skyscan) was used to provide 3D images.

### Histological staining

Detailed histological staining protocols can be found in our previous study. In brief, specimens were fixed in 10% neutral buffered formalin, then embedded in paraffin and 5 mm sections were cut, collected on slides, and stained with hematoxylin and eosin (H and E; Sigma) for histological evaluation. Alcian blue (Sigma) staining was used for proteoglycan detection according to the standard protocol. Masson's trichrome staining was used for collagen fiber detection according to the standard protocol.

### Statistical analysis

All statistical evaluations were performed by a professional qualified statistician. Mean, standard deviation (SD), and range were calculated and were expressed as means  $\pm$  SD by three experiments ( $n = 3$ ) for each test. The control and experimental groups were compared with each other by *t*-test.  $P < 0.05$  was considered statistically significant.

## Results

### Gross evaluation of osteonecrosis specimens

The ONFH repair potential of our method was studied in a rat model. Three groups (CON, PTH-H [10  $\mu$ g/kg], and PTH-L [1  $\mu$ g/kg]) were established for comparison. To identify the dose effects, two concentrations were chosen in this animal model. All the rats behaved as usual in all three groups. There was no nausea, vomiting, diarrhea, or bleeding tendency in all three groups. The body weight of rats increases the same extend in all rats. Eight weeks after surgical operation, all animals were sacrificed for gross evaluation and other examinations. Gross evaluation revealed that the collapse of the femoral head could be easily observed in the control group [Figure 1a]. The opposite was seen in the PTH-H [Figure 1b] and PTH-L groups [Figure 1c]. The femoral heads of both groups maintained their spherical shape. Radiographic examination was performed as well. The femoral heads of the three groups showed results similar to the gross examination [Figure 1d-f]. These experimental results suggested that intermittent PTH injection might play a crucial role in preventing the collapse of the femoral head. We thought that intermittent PTH injection would prompt osteogenesis and decrease femoral head collapse.

### Histological staining

H and E staining showed trabecular bone and articular cartilage in the specimens [Figure 2]. Collapse and degeneration of the articular surface was also seen in the control group [Figure 2]. However, the articular

surface was obviously maintained in the intermittent PTH injection groups, compared to the control group, but it was more intact in the PTH-H group than in the PTH-L group. In addition, the large lacuna in the trabecular bone area showed a trend toward collapse of the femoral head in the control group. There were more osteoblasts in the trabecular lacuna of the PTH-H group than of the PTH-L group [blue arrows in PTH-H group of Figure 2].

Masson's trichrome staining clearly showed the areas of bone necrosis and osteolysis on the acetabular surface of the specimens. Large areas of bone necrosis and osteolysis were seen in the control group, compared to the intermittent PTH injection groups [white arrows in CON group of Figure 3]. Masson's trichrome staining also showed the collagen fiber distribution. More osteolysis areas in the control group than in the intermittent PTH injection groups showed collagen fibers of bone tissue [black arrows in Figure 3]. Furthermore, trabecular areas of acetabular bone revealed thin bone areas delimiting

enlarged lacunar spaces in the control group, compared to the intermittent PTH injection groups [green arrows in Figure 3]. Comparisons of the two PTH-H groups with regard to the points mentioned above revealed that high-dose intermittent PTH injection was more effective than low-dose intermittent PTH injection.

Safranin-O staining revealed the presence of acidic proteoglycan in cartilage tissues, indicating cell chondrogenesis. The PTH-H group showed the integrity and intense safranin-O staining of the cartilage layer [blue arrows in Figure 4]. However, intense safranin-O staining of the cartilage layer was also observed in the PTH-L group, and the degeneration and cartilage lesion still appeared in the group [green arrows in Figure 4]. Furthermore, the large amount of acidic proteoglycan loss of safranin-O staining was clearly shown in the control group [black arrows in Figure 4]. These histological staining results again proved that intermittent PTH injection might play a crucial role in preventing the collapse of the femoral head.

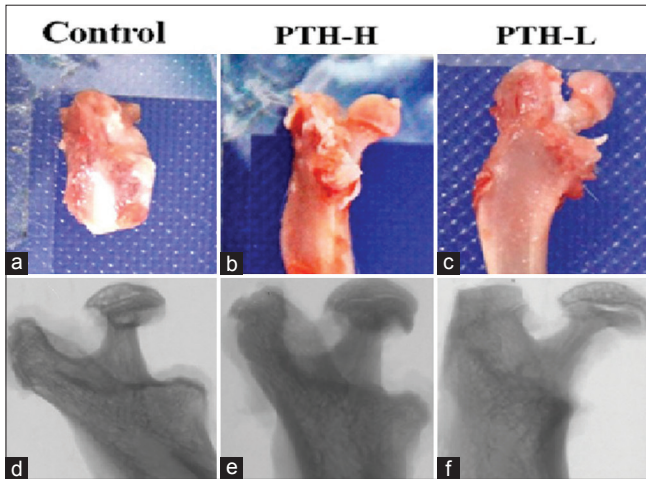


Figure 1: Gross evaluation of femoral heads (a-c). Micro-CT view of femoral heads (d-f)

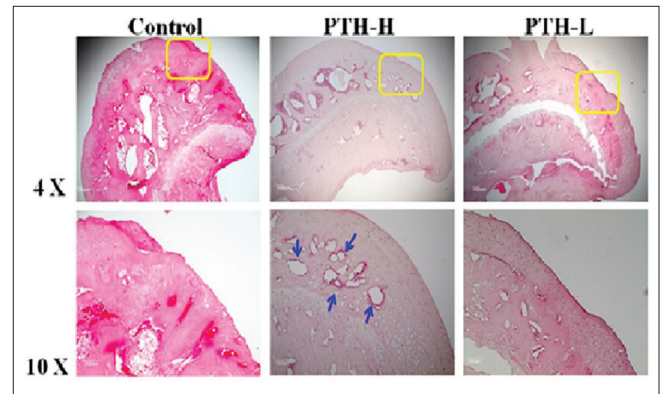


Figure 2: H and E staining showed trabecular bone and articular cartilage in the CON, parathyroid hormone-H, and parathyroid hormone-L groups. The circled areas were shown on the bottom. The blue arrows showed osteoblasts in the trabecular lacuna

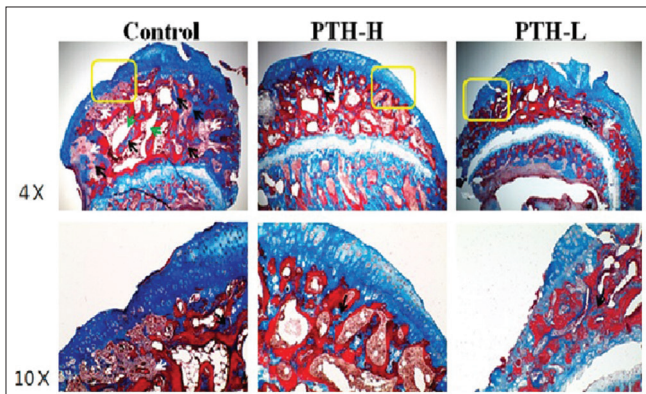


Figure 3: Masson's trichrome staining showed the areas of bone necrosis and osteolysis and collagen fiber distribution in the CON, parathyroid hormone-H, and parathyroid hormone-L groups. The circled areas were shown on the bottom. The white, black, and green arrows were indicated the bone necrosis and osteolysis, collagen fiber distribution, and delimiting lacunar spaces, respectively

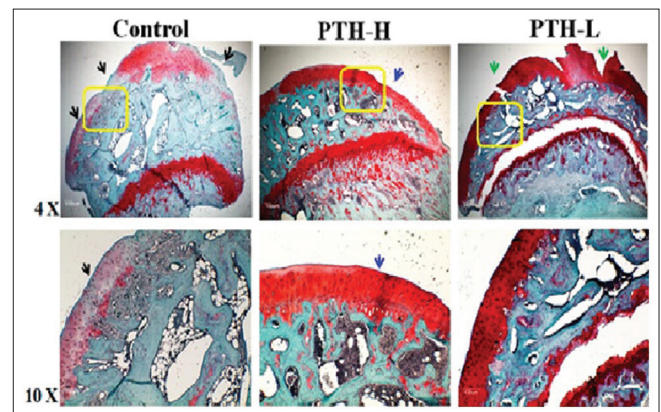


Figure 4: Safranin-O staining revealed the presence of acidic proteoglycan in cartilage tissues in the CON, parathyroid hormone-H, and parathyroid hormone-L groups. The circled areas were shown on the bottom. The blue, green, and black arrows were indicated the integrity cartilage layer, degradation and cartilage lesion, and acidic proteoglycan loss, respectively

### Micro-computed tomography examination

A  $\mu$ -CT examination was further performed to examine the potential of intermittent PTH injection in the rat model. Five indicators, i.e., bone volume (BV), BV ratio, Trab-Th, Trab-Th ratio, and BMD were analyzed. Two types of analysis were used, one for the right femoral heads for nonsurgical operation and another for the left femoral heads for surgical operation [Table 1]. The values of BV, BV ratio, and BMD showed similar trends whether right femoral heads or left femoral heads, respectively. The  $\mu$ -CT results showed that bone formation occurred in a PTH dose dependent manner, i.e., PTH-H group > PTH-L group > CON group ( $P < 0.05$ ). In addition, the values of Trab-Th and Trab-Th ratio showed that bone formation occurred in a PTH dose dependent manner in the right femoral heads ( $P < 0.05$ ). However, the Trab-Th value showed no significant differences in the left femoral heads ( $P < 0.05$ ) as well as the value of Trab-N, and the Trab-Th ratio of the left femoral heads revealed a trend opposing that of the right femoral heads. Interestingly, the value of Trab-N in the right femoral heads revealed the trend opposing that values of Trab-Th ( $P < 0.05$ ).

### Discussion

PTH is an anabolic agent that induces bone formation when given in an intermittent manner. The early report had indicated that the possible mechanism for PTH action is its stimulation of the proliferation and differentiation of bone marrow osteoprogenitor cells to osteoblasts after PTH administration for 1 week.<sup>13</sup> Davies and Chambers showed that PTH promotes the adhesion of endogenous bone marrow MSCs to the trabecular bone surface by *in vitro* study and *in vivo* animal experiment.<sup>14</sup> We thought that PTH would increase the numbers of MSCs and enhance their recruitment to bone resorption sites although the study did not measure this aspect. Another concept supporting our study is that intermittent PTH injection could promote angiogenesis in recent researches. Kang *et al.* showed that intermittent PTH could reverse radiation-induced osseous hypovascularity by promoting angiogenesis.<sup>15</sup> Zhou *et al.* used intermittent PTH to treat rabbit steroid-associated osteonecrosis.<sup>16</sup> Osteogenesis and neovascularization are

proved by histology and elevation of serum marker. Our prospective study revealed a promising anabolic effect of intermittent PTH injection in the rat model with ONFH. Intermittent PTH injection not only decreased femoral head collapse in the vascular deprivation model of rat femoral head but also increased the bone density level in the postoperative period. High PTH concentrations had stronger anabolic effects than the control group and the low concentration group. Although no previous study has proved that intermittent PTH injection could treat ONFH, we believe that PTH could stimulate osteogenesis in the ischemic bone environment.

Nowadays, the clinical use of teriparatide is 20  $\mu$ g/day. From previous study, teriparatide 40  $\mu$ g/day could increase bone marrow density >20  $\mu$ g/day.<sup>17</sup> The effects of fracture risk are the same in both groups, but 40  $\mu$ g group may have higher rate of side effect. Based on these studies, we can estimate that the effective dosage of teriparatide is around 0.2–1  $\mu$ g/kg/day if we assume that the body weight of normal person is around 40–100 kg. We could find many different protocols of PTH injection in rat model.<sup>18–20</sup> All these experiments showed good anabolic effect of intermittent parathyroid injection. We could estimate that the average dosage of these studies is around 10–20  $\mu$ g/kg/day. From above information, we set our experiment group PTH-H 10  $\mu$ g/kg and PTH-L 1  $\mu$ g/kg. Besides, it is much easier to prepare PTH solution with ten times differences.

Intermittent PTH administration actually has been used in osteoporosis and fracture healing for many years.<sup>10–12</sup> Several studies have used PTH to manage the long term complications of bisphosphonates: atypical fracture and osteonecrosis of the jaw. Atypical fracture is a kind of stress fracture with an abnormal fracture remodeling process induced by bisphosphonates.<sup>21</sup> These patients usually have thigh pain for times with a bird beak sign in the X-ray of the femoral shafts. However, there was still controversy about the management of incomplete atypical fracture and postoperative antiosteoporosis medication. Chiang *et al.* collected 14 patients with atypical fractures.<sup>22</sup> Five of them completed teriparatide treatment for 6 months. Increased bone remodeling

**Table 1: The analysis results by micro-computed tomography**

Group	BV	BV ratio	Trab-Th	Trab-Th ratio	Trab-N	BMD
C-L	3.87±0.54	0.31 <sup>a</sup>	0.13±0.02	0.82 <sup>a</sup>	2.94±0.02	0.59±0.06
C-R	12.60±0.53	1 <sup>b</sup>	0.16±0.01	1 <sup>b</sup>	3.11±0.01	0.74±0.01
PTH-H-L	5.11±1.70	0.45 <sup>c</sup>	0.14±0.03	0.60 <sup>c</sup>	3.56±0.06	0.72±0.04
PTH-H-R	11.40±0.50	0.90 <sup>d</sup>	0.23±0.05	1.49 <sup>d</sup>	3.33±0.02	0.89±0.07
PTH-L-L	4.49±0.65	0.42 <sup>c</sup>	0.13±0.01	0.71 <sup>c</sup>	3.27±0.06	0.66±0.02
PTH-L-R	10.63±0.97	0.84 <sup>f</sup>	0.19±0.03	1.20 <sup>f</sup>	3.61±0.03	0.85±0.03

<sup>a</sup>C-L/C-R; <sup>b</sup>C-R/C-R; <sup>c</sup>H-L/H-R; <sup>d</sup>H-R/C-R; <sup>e</sup>L-L/L-R; <sup>f</sup>L-R/C-R. C-L=Control group-left femoral head, C-R=Control group-right femoral head, H-L=High-dose group-left femoral head, H-R=High-dose group-right femoral head, L-L=Low-dose group-left femoral head, L-R=Low-dose group-right femoral head. BMD=Bone mineral density, BV=Bone volume, PTH=Parathyroid hormone, Trab=Thyroid-stimulating hormone receptor antibody

markers and improved fracture healing were found in all five patients. The less densely mineralized bone increased in proportion to the distal radius and distal tibia in the  $\mu$ -CT examination compared to the control group. Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a rare condition with long term use of bisphosphonate.<sup>23</sup> Intravenous form of nitrogen-containing bisphosphonate had a higher incidence rate than the oral form.<sup>24</sup> Most cases of BRONJ could be managed conservatively; however, there were still some BRONJ patients suffering from poor wound healing with repeated debridement. In recent years, intermittent PTH injections have been used in the management of BRONJ, with good results because of the strong anabolic effect of PTH.<sup>25,26</sup> Although the etiology of ONFH, BRONJ, and atypical fracture is different, we believe that intermittent PTH injection could create a new bone micro-environment to stimulate osteogenesis.

Several rat ONFH models were proposed based on different etiologies. Kerachian *et al.* first successfully induced rat ONFH by glucocorticoid injection without surgical intervention.<sup>27</sup> However, different species of rats showed different susceptibilities to developing ONFH after 90 days of subcutaneous injection of glucocorticoid. Okazaki *et al.* proposed an alcohol-induced rat ONFH model by feeding a liquid diet containing 5% ethanol.<sup>28</sup> Osteonecrotic change of the rat femoral head could develop 1 week after feeding a 5% ethanol liquid diet. The precise accumulated dosage and duration of ethanol feeding needed to induce rat ONFH are still unclear. Norman *et al.* first proposed a vascular deprivation-induced rat ONFH model using surgical incision of the ligamentum teres and periosteum around the femoral neck.<sup>1</sup> All rats showed the same osteonecrotic change, according to the experimental results. Necrosis of the adipose and hematopoietic cells was evident as early as the 2<sup>nd</sup> postoperative day in the microscopic examination. Necrosis of the subchondral and trabecular bone occurred around the 5<sup>th</sup> postoperative day. Complete replacement of all the necrotic tissue by living bone occurred after 6 weeks. We chose a vascular deprivation-induced rat ONFH model because of the highly consistent response rate. Our results also revealed the same osteonecrotic change in the same group of rats.

The results of nonsurgical treatment are poor in the late stage of ONFH. In the early stage of ONFH, necrotic bone must be removed, and then, new bone can begin to generate. Femoral head collapse occurs when the bone repair process is slower than the bone resorption process. Therefore, most research tried to control ONFH progression in the early stage with medication reestablishing equilibrium between osteoclasts and osteoblasts. Alendronate, a third-generation bisphosphonate, has the function of reducing the bone turnover rate by inhibiting osteoclast activity. Several studies have shown that alendronate could be effective in an animal ONFH model,

including rat and rabbit.<sup>5,29</sup> Alendronate also showed good clinical results in the management of early human ONFH in studies during the past 10 years.<sup>30,31</sup> However, a recent 2-year, multicenter, prospective, randomized, double-blind, and placebo-controlled study revealed that alendronate has no effect on preventing the necessity for total hip arthroplasty, reducing disease progression, or improving life quality.<sup>32</sup> Hyperbaric oxygenation (HBO) showed the ability to inhibit osteoclast activity through reduction of RANKL expression.<sup>33</sup> HBO actually had a more pronounced antiosteoclast effect than hyperbaric pressure or normobaric hyperoxia. The trial use of HBO in early-stage ONFH patients also showed good clinical results after 6 weeks.<sup>34</sup> Extracorporeal shockwave therapy (ESWT) induced ingrowth of neovascularization with increasing expression of endothelial nitric oxidase and vessel endothelial growth factor and promotion of osteogenesis in animal models.<sup>35</sup> Based on its strong anabolic effect on bone tissue, ESWT alone revealed good clinical results in the management of early-stage ONFH patients compared to combined therapy with alendronate or vascular bone grafting.<sup>36</sup> Although HBO and ESWT, such as alendronate, had positive results in early-stage ONFH in the literature, there is still no high-level evidence to prove their efficacy and efficiency.

There are several limitations in this study. First, no previous research has proved that intermittent PTH has either a positive or negative effect on ONFH in the rat model. Our study should be regarded as a pilot study. Although high-concentration PTH preserved more femoral head than low-concentration PTH, the ideal concentration and duration of PTH treatment for ONFH are still unknown. Second, the sample size of our rat study is small. This could result in weak power in the statistical study. Third, the femoral head size varied due to the different age and gender of our rats. The effect of this could be reflected by the relatively high variance of bone volume of the femoral head. Therefore, we measured the ratio between the right (ONFH) and left (control) femur bone volume to minimize individual differences. Fourth, the weight-bearing status of the ONFH rat may affect the progression of femoral head collapse. Although we did not control all the rats in terms of the same weight-bearing status, the final result did not show a significant difference in the same study group. In other words, all the rats should have the same control variables in the postoperative period.

## Conclusion

From this study, we concluded that intermittent PTH could decrease femoral head collapse in ONFH in the rat model. High PTH concentration has more protective effect on the femoral head than a low concentration of PTH. We also suggest that  $\mu$ -CT could be a good evaluation tool for ONFH in the animal model.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

## Financial support and sponsorship

This research was supported by research program of Taipei Medical University Hospital. The research project name is 103TMUH-NE-02.

## Conflicts of interest

There are no conflicts of interest.

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