The effect of administration of parathyroid hormone (1-34) on sinus bone graft & dental implant in ovariectomized rabbits

Chugeum Dam

Department of Dentistry

The Graduate School, Yonsei University

The effect of administration of parathyroid hormone (1-34) on sinus bone graft & dental implant in ovariectomized rabbits

Directed by Professor Wonse Park

A Doctoral Dissertation
submitted to the Department of Dentistry
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree of
Doctor of Philosophy

Chugeum Dam

June 2017

연세대학교
YONSEI UNIVERSITY

This certifies that the Doctoral Dissertation
of Chugeum Dam is approved.

Thesis Supervisor : Wonse Park

Kee-Deog Kim

Bock-Young Jung

Ui-Won Jung

Hyun Sil Kim

The Graduate School

Yonsei University

June 2017

감사의 글

많이 부족한 제가 여러 고마운 분들의 도움으로 학위논문을 마무리할 수 있게 되어 감사의 말씀을 전합니다.

먼저 저에게 너무나 좋은 기회를 주시고 많이 참고 많이 기다려주신 박원서 교수님 진심으로 감사 드립니다. 수련의가 된 그날부터 교수님의 많은 배려가 있었기에 오늘의 제가 있습니다. 바쁘신 와중에도 논문 심사를 맡아주시고 조언을 아끼지 않으신 김기덕 교수님, 정복영 교수님, 정의원 교수님, 김현실 교수님께도 마음 깊이 감사 드립니다. 제가 처한 상황을 잘 이해해 주시고 많은 위로와 격려를 주신 방난심 교수님 항상 감사 드립니다. 학부 때부터 많은 관심과 조언 주신 황충주 교수님 감사 드립니다.

전반적인 실험과 논문에 큰 도움 준 박경미, 김서율 연구원에게도 많이 감사하고 미안했던 마음을 전합니다. 연구 및 논문 작성 과정에서 실질적인 조언을 아끼지 않고 길잡이가 되어준 허지선, 김윤미, 임지영 박사님도 마음 깊이 감사합니다. 힘들 때 많은 위로와 격려를 준 최은혜, 이강희, 김민유, 양형주 선생님 감사합니다.

또한 제가 대학원을 다닐 수 있게 배려해주시고 연구 및 논문 쓰는 과정에서도 물심양면 도움과 격려를 아끼지 않으신 세란치과 조문건 원장님께 깊이

감사 드리며, 원장님 가족 분들과 세란치과 식구들께도 감사의 말씀을 전합니다.

포기하고 싶었던 모든 순간 가장 가까이에서 채찍질해주고, 모든 고민을 함께 해준 남편에게 고맙다는 말을 전하고 싶고, 뱃속에서 대학원을 함께 다닌 큰딸 시원이, 논문을 함께 쓴 작은딸 소원이, 너희 존재만으로도 큰 힘을 얻었고 너희에게 자랑스러운 엄마가 되고 싶다는 생각으로 마무리 할 수 있었단다. 저의 도움 요청에 한걸음에 달려와주신 친정엄마, 너무 좋은 할머니가 되어주신 덕분에 제가 논문을 쓸 수 있었습니다. 엄마 딸로 태어난 건 제 행운의 시작이며 항상 감사하고 사랑합니다. 항상 제 걱정 해주시는 할아버지와 듬직한 오빠 그리고 언제나 힘이 되어준 친정 시댁 모든 가족 구성원들에게 감사의 마음을 전합니다.

마지막으로 저의 박사학위 취득을 누구보다 자랑스러워하며 크게 기뻐하셨을 아버지께, 너무 늦어서 죄송하고, 하늘에서 미소 짓고 계실 것으로 생각하며 이 논문을 바칩니다.

2017년 06월

담추금 씀

CONTENTS

List of Figures

List of Tables

Abstract

The effect of administration of parathyroid hormone (1-34) on sinus bone graft & dental implant in ovariectomized rabbits

Chugeum Dam

Department of Dentistry
The Graduate School, Yonsei University
(Directed by Professor Wonse Park, D.D.S., Ph.D.)

Purpose: The purpose of the present study is to investigate the effect of administering intermittent parathyroid hormone[Teriparatide , PTH (1-34)], on the maxillary sinus lift and bone graft in osteoporosis-induced rabbits.

Materials and Methods: Twenty female New Zealand white rabbits were received ovariectomy. The animals were randomly divided into two groups: **PTH** group (*n* =10); 10 μg/kg/day PTH was injected subcutaneously 5 days a week for 5 weeks (1 week before, 4 weeks after sinus surgery). **Saline** group (*n*=10); same dose and duration of saline was injected. In maxillary sinus surgery, bone graft with Bio-oss® was augmented into 13 sinuses, and bone grafts and implants were simultaneously performed in 7 sinuses. Animals were sacrificed 4 weeks after surgery. To determine whether PTH was effective

for osteoporosis, we measured the BMD of the right femur using microCT, and performed radiographic and histometric analysis of the maxillary sinus surgery site. Statistics used Mann-Whitney test.

Result: BMD increased in the femur, but in sinus, all parameters of radiographic and histometric analysis showed no significant difference between the groups, and the difference between individuals was even greater.

Conclusion: Intermittent PTH might not promote new bone formation in the augmented maxillary sinus of ovariectomized rabbits.

Key words: teriparatide, parathyroid hormone, sinus augmentation, rabbit sinus model, ovariectomy

The effect of administration of parathyroid hormone (1-34) on sinus bone graft & dental implant in ovariectomized rabbits

Chugeum Dam

Department of Dentistry

The Graduate School, Yonsei University

(Directed by Professor Wonse Park, DDS, PhD)

Ⅰ. Introduction

A vertical bone deficiency with pneumatization of the sinus is frequently found in the teeth loss site of posterior maxilla, and the sinus bone graft technique has been greatly advanced in the previous century to overcome the limitations of implantation in this site. During sinus lift and bone graft, implantation may be simultaneously performed or the installation may be delayed for a sufficient period of time, which depends on the quality of the maxillary alveolar bone and the vertical and horizontal quantity of the remaining

bone. In both of the methods, a considerably long times is needed until the bone graft material undergoes new bone formation for at least four to six months[1,2] or even from seven to twelve months.[3-5]

Osteoporosis is the most common systemic disease that interferes bone graft healing. In particular, bone mineral density (BMD) is one of the critical factors to implant integration failure after bone graft.[6] A patient having a low BMD due to osteoporosis has a higher chance of bone graft failure.

When new bone formation is delayed or fails and thus the treatment period is increased, the period of time when the patient is unable to masticate with the posterior teeth is increased. This may cause supra-eruption and periodontal problems at the opposite teeth and the bite force may be concentrated in another teeth remaining. To investigate the method of reducing the period needed for bone healing, we focused on human parathyroid hormone [Teriparatide , PTH (1-34)], which is an osteoporosis drug having an anabolic effect.

Most of the currently used osteoporosis drugs are antiresorptive agents that increase bone density by inhibition of osteoclast activity. In contrast, intermittent administration of the PTH 1-34 (teriparatide) injection enhances bone formation by increasing osteoblast activity.[7-13] It is more effective to increase BMD in postmenopausal women, men who diagnosed with osteoporosis, and steroid-induced osteoporosis patients than bisphosphonate.[14-17]

Many previous studies have shown that the intermittent administration of PTH increases systemic bone mass, strength, and BMD,[18,19] prevents bone loss,[20] helps bone fracture healing,[21,22] and also reverses the number and activity of osteoblast that are reduced by radiotherapy.[23] In dentistry, the intermittent administration of PTH inhibits periodontitis by preventing alveolar bone loss,[24,25] enhances osseous wound healing,[26] and prevents and treats medication related osteonecrosis of the jaw (MRONJ).[27-29] The intermittent administration of PTH also enhances bone formation of the implants and bone graft materials used in orthopedics and dentistry.[30-41]

On the basis of the previous studies showing that PTH increases BMD and helps implant osseointegration, Huh.et al.[42] investigated the effect of PTH following sinus lift and bone graft in healthy female rabbits and reported that PTH did not have a significant effect on sinus new bone formation. We consider that the homeostasis of the other bone formation factors was maintained in healthy animals. Therefore, we established a hypothesis that PTH, although ineffective in the healthy population, may be effective in osteoporosis model, and then evaluate PTH in osteoporosis-induced ovariectomized rabbits. The purpose of the present study is to investigate the effect of PTH on the maxillary sinus lift and bone graft in osteoporosis-induced rabbits.

Ⅱ. Materials & Methods

1. Animals

Twenty female New Zealand white rabbits (body weight 2.8-3.2㎏) were used in this study. All the laboratory animals were raised and managed by the Department of Laboratory Animal Resources in Avison Biomedical Research Center at Yonsei University College of Medicine. The experiment was performed according to the certification standards of the International Association for Assessment and Accreditation of Laboratory Animal Care (IACUC Approval No. 2014-0069). The animal breeding facility was kept at the temperature of 20℃ ± 5℃ and relative humidity of 50% ± 10%, and the standard laboratory diet was fed to the animals. Water and food was freely supplied, and a 12-hour light-dark cycle was maintained. The experiment began following one week of acclimation period for the laboratory animals. Sample size calculation was using G Power (Ver.3.1.9.2, Faul, Erdfelder, Lang and Buchner.) software. Reference to Choi et al. in 2012[43], with 95% power, 0.05 alpha level and 5% within-group standard deviation. This resulted in 8 rabbits being used in the present study. So we experimented with 10 rabbit with dropout set at 20%.

2. Experiment design

The rabbits after the acclimation period underwent ovariectomy (OVX), and steroid was administered to the rabbits for 28 days (prednisolone, Samu median, Yesan, Korea; 1

㎎/㎏/day, daily for 28 days, SC) after two weeks of resting. After the completion of the steroid administration, ten rabbits administered with a saline vehicle solution were allocated to a control group, while other ten rabbits administered with teriparatide (FORSTEO®, Eli Lilly, Houten, the Netherlands; 10 ㎍/㎏/day, 5 days weekly for 5 weeks, SC) were allocated to an experimental group. The period of administration was totally five weeks, including one week before maxillary sinus operation and four postoperative weeks. In the maxillary sinus operation, Bio-Oss® particles (Geisthlich Pharma AG, Wolhusen, Switzerland; particle size 0.25-1 ㎜) were grafted to the right and left maxillary sinus, while custom made cylinder type mini implant (Dentium, Seoul, Korea; diameter 3 ㎜, length 6 ㎜) were simultaneously implanted to the right maxillary sinus in seven rabbits. As a result, the number of maxillary sinus that underwent only bone graft was 13 in the experimental group and 13 in the control group. The number of maxillary sinus that underwent implantation was 7 in the experimental group and 7 in the control group. After four weeks of sinus surgery, the animals were scarified. **(Figure 1)**

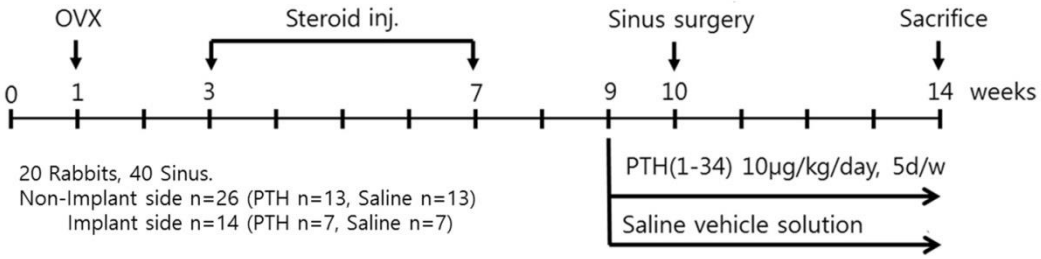

Figure 1. Experimental design.

3. Surgical Procedure

After general anesthesia via zoletil (tiletamine and zolazepam, Virbac Laboratories, Carros, France; 15 ㎎/㎏, SC) and Rompun (xylazine, Bayer, Leverkusen, Germany; 5 ㎎/㎏, IM), the nasal bone area was shaved. Local anesthesia was performed at the surgical region by using 2% lidocaine (LidocaineHCl, Huons, Seoul, Korea), and the surface was sterilized by using povidone. Then, straight incision was performed along the sagittal midline on the nasal bone. After that, the full-thickness flap was elevated. According to the rabbit sinus model proposed by Choi et al.[43] in 2012, a circular window was formed at both sides at the position 20 mm from the nasofrontal suture and 10 mm lateral from the midline by using 6 mm trephine bur (C-reamer, Neobiotech, Seoul, Korea) under saline solution irrigation. Then, the resected bony disc was carefully removed, and the maxillary sinus membrane was elevated to form a maxillary sinus bone graft site. Drilling (2.7 ㎜ in diameter) was performed for implantation at a position 3 ㎜ from

the window only at the right side, and then Bio-Oss 0.1 g was weighed and grafted at both sides but the implantations was performed only at the right side. After completing all surgical procedures, the body disc was relocated, and the periosteum and skin were sutured by using glyconate absorbable monofilament. (6-0 Monosyn, B-Braun, Aesculap, Allentown, PA, USA). **(Figure 2)**

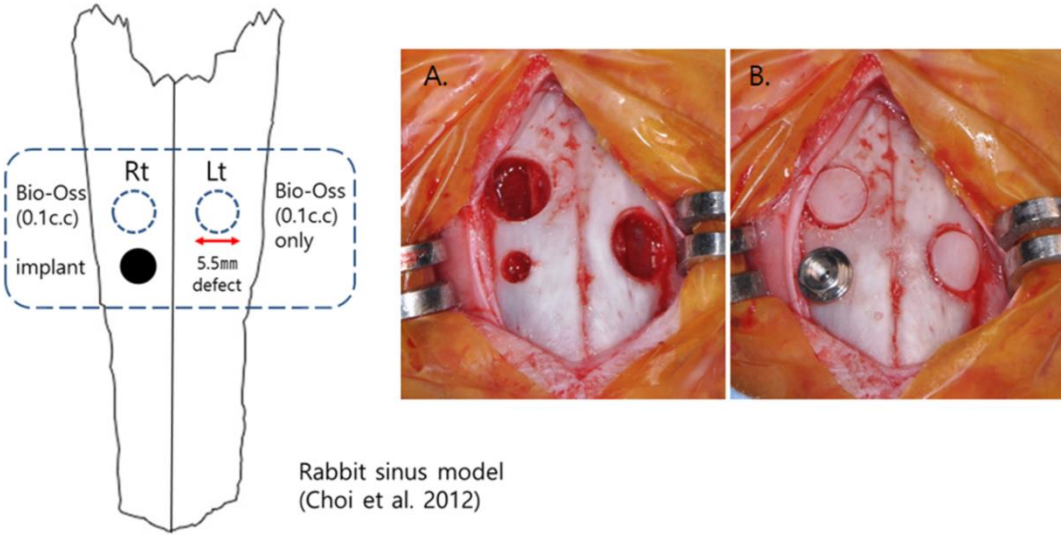

Figure 2. Surgical procedure of ovariectomized rabbit sinus. (A) Bony window and Schneiderian membrane. (B) Bone grafted with implant.

4. Postoperative treatment and sacrifice

An anti-inflammatory drug (ketorolac; 0.5 ㎎/㎏, IV) was administered once for pain control. A broad-spectrum antibiotic (enrofloxacin; 5 ㎎/㎏, once a day for 5 days, SC) was administered for infection control. The surgical region was stitched out one week after the operation. Saline and PTH were subcutaneously injected to respectively groups according to the predetermined administration schedule, and deep anesthesia was induced in the postoperative Week 4 and then KCl was intravenously injected to sacrifice the animals. Block section was performed including the bone graft region, the implantation region, and the surrounding bone, and the sectioned part was fixed by dipping in 10% formalin for 14 days.

5. Radiographic analysis; Microcomputed tomography

- **Long bone :**

Images of a total of 20 right side distal femurs were taken by using high resolution micro-computed tomography (Skyscan 1173, Skyscan, Konitch, Belgium). The volume of interest (VOI) was set in a direction vertical to the long axis to 10 mm from the end of growth plate. **(Figure 3)** The bone mineral density (BMD), percent bone volume (BV/TV, bone volume/tissue volume), trabecular thickness (Tb.Th), trabecular number (Tb.N), and trabecular separation (Tb.Sp) were measured in the volume of interest on the trabecular bone in each group through micro-CT imaging and analysis. (greyscale value: 83-255)

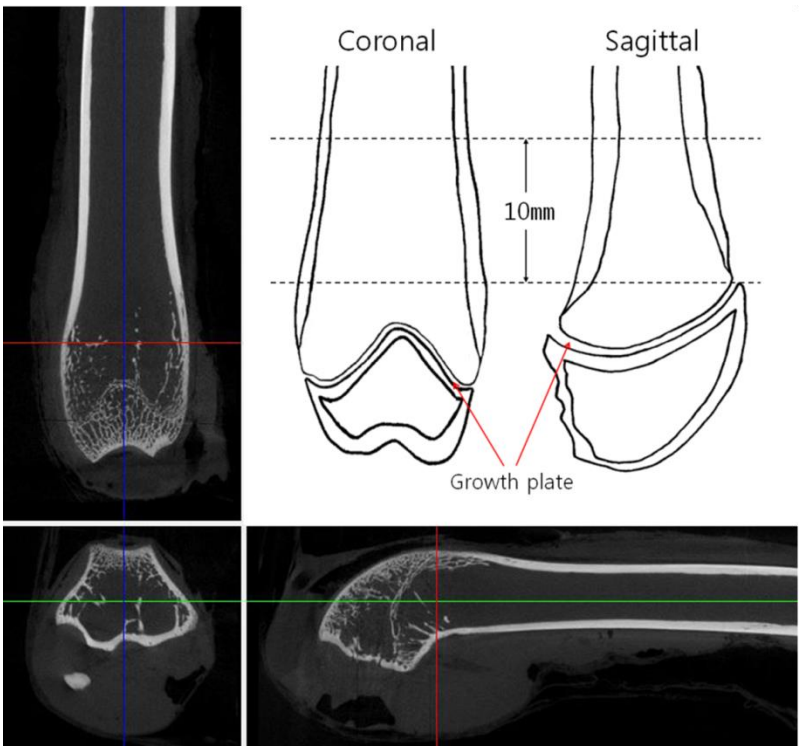

Figure 3. Microcomputed tomography (microCT) analysis of distal femur. The volume of interest (VOI) was set in a direction vertical to the long axis to 10 mm from the end of growth plate.

- **Sinus :**

Micro-CT images of the sectioned sinus block specimens were taken under the conditions of 130 ㎸, 60 ㎛, and 17.86 ㎛ pixel size. The images were processed with CTAn (Skyscan, Aartselaar, Belgium). The total bone volume (TBV, ㎣), grafted bone volume (GBV, ㎣), and new bone volume (NBV, ㎣) were measured in the VOI that

was set to be the entire sinus including the grafted material and newly formed tissue. (grayscale value: total bone 72-255, graft bone 90-255, new bone 72-90) **(Figure 4)**

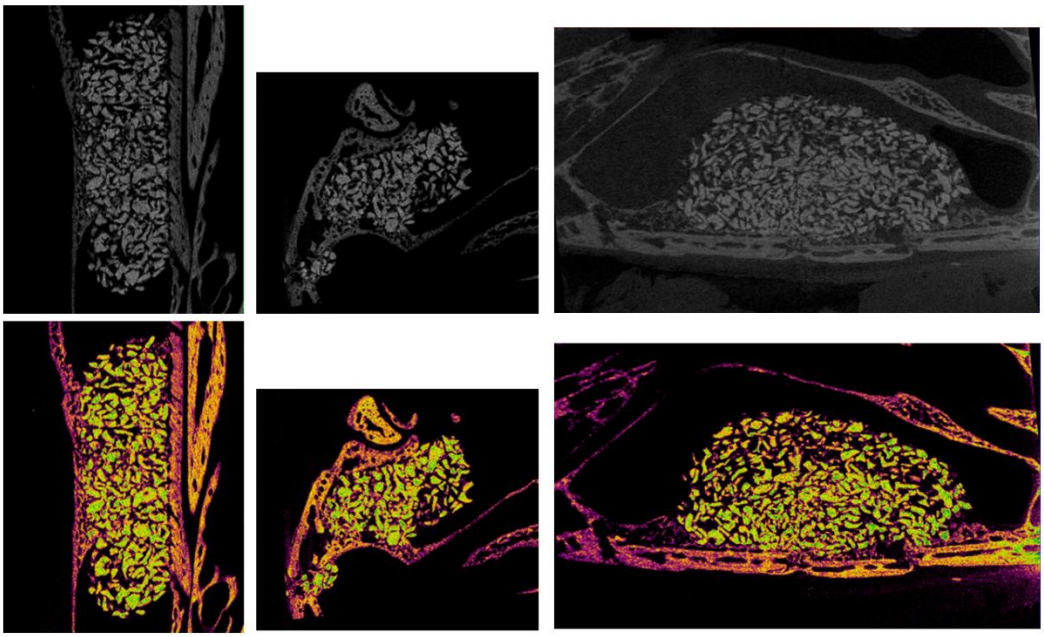

Figure 4. Microcomputed tomography (microCT) analysis of sinus. Grayscale (upper) and color (lower) images. Axial, coronal and sagittal views (left to right). In the color images, yellow-green and purple represent bone substitute material and newly formed bone, respectively.

6. Histomorphometric analysis

After the micro-CT scanning, the specimens were demineralized by dipping into a 5% formic acid solution, embedded with paraffin, and then serially sectioned in a thickness of

5 ㎛. In the bone graft only specimens, coronal section was performed at the center of the window. In the bone graft with implant specimens, Sagittal section was performed at the center of the implant. The tissue samples passing through the core of window or implant were selected and stained by hematoxylin-eosin staining and Masson's trichrome staining. Then, the samples were scanned at x100 magnification by using a light microscope (Leica DM 2500, Leica Microsystem, German and Virtual microscope VS120, Olympus Corporation, Japan).

- **Area measurements**

The area in the images was measured by using the Adobe Photoshop software (Adobe Photoshop CS4., Mountain View, CA, USA). Firstly, the total augmented area (TAA) was identified, and the new bone area (NBA), residual material area (RMA), and fibrovascular tissue area (FTA) was measured. Then, the ratios of NBA, RMA, and FTA in the TAA were calculated. **(Figures 5 and 6)** Additionally, high magnification images (x 200) of the regions near the window, the Schneiderian membrane, and the center of the augmented area were obtained, and the ratios of NBA, RMA, and FTA were calculated for the regions. **(Figure 7)**

- **Linear measurements**

Image-Pro Plus (Media Cybernetics, Silver Spring, MD, USA) was used to measure the length of the individual elements of the implant side. The method referred to the study

of Jung et al.[44], six items of the linear measurement were the anterior and posterior cortical bone height (CBH Ant. an CBH Pos.), protruding height (PH), augmented height (AH), and anterior and posterior osseointegration height (OH ant., OH pos.). **(Figure 8)**

All the tissue measurement was performed in a blind manner by two observers by randomly mixing the samples from the experimental group and the control group. The intraclass correlation coefficients (ICCs) of all the elements were measured to examine the interobserver reliability. The data having an ICC value from 0.8 to 1.00 were considered as reliable.

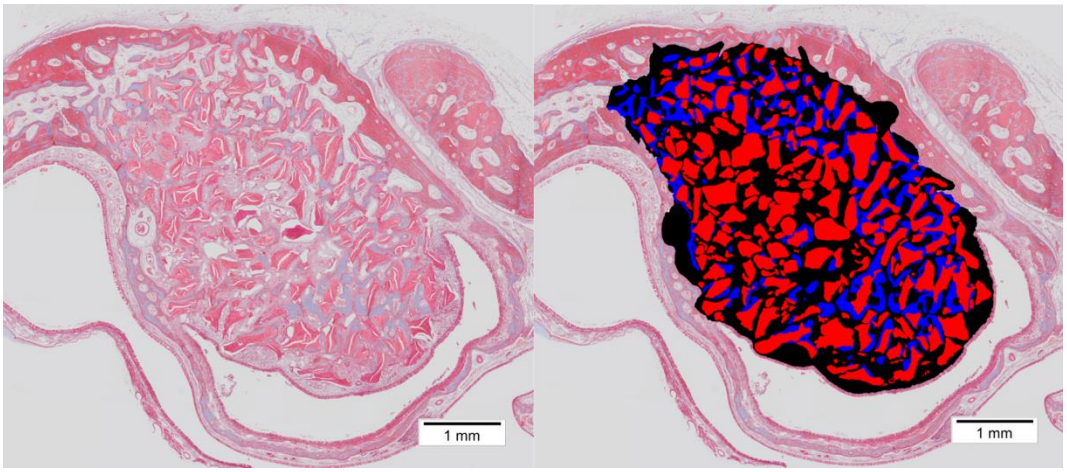

Figure 5. Non-implant side histomorphometric analysis. Total augmented area (black), New bone area (blue), residual material area (red).

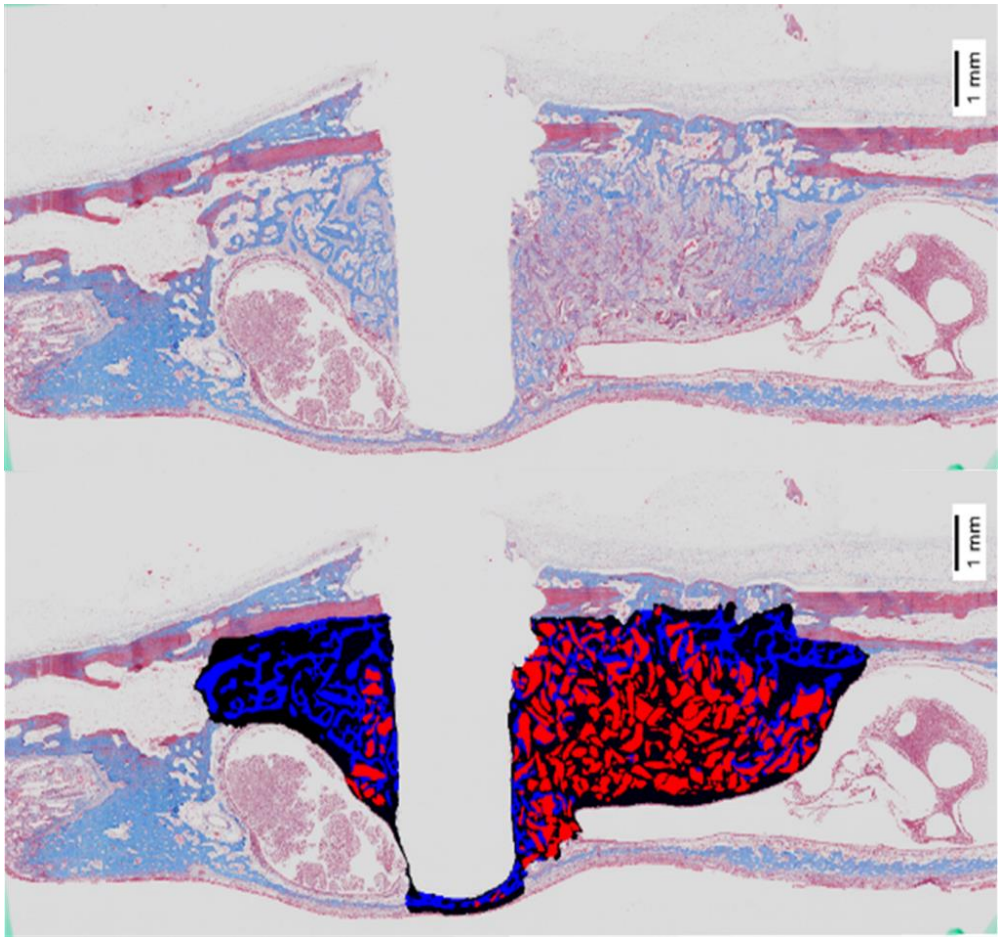

Figure 6. Implant side histomorphometric analysis. Total augmented area (black), New bone area (blue), residual material area (red).

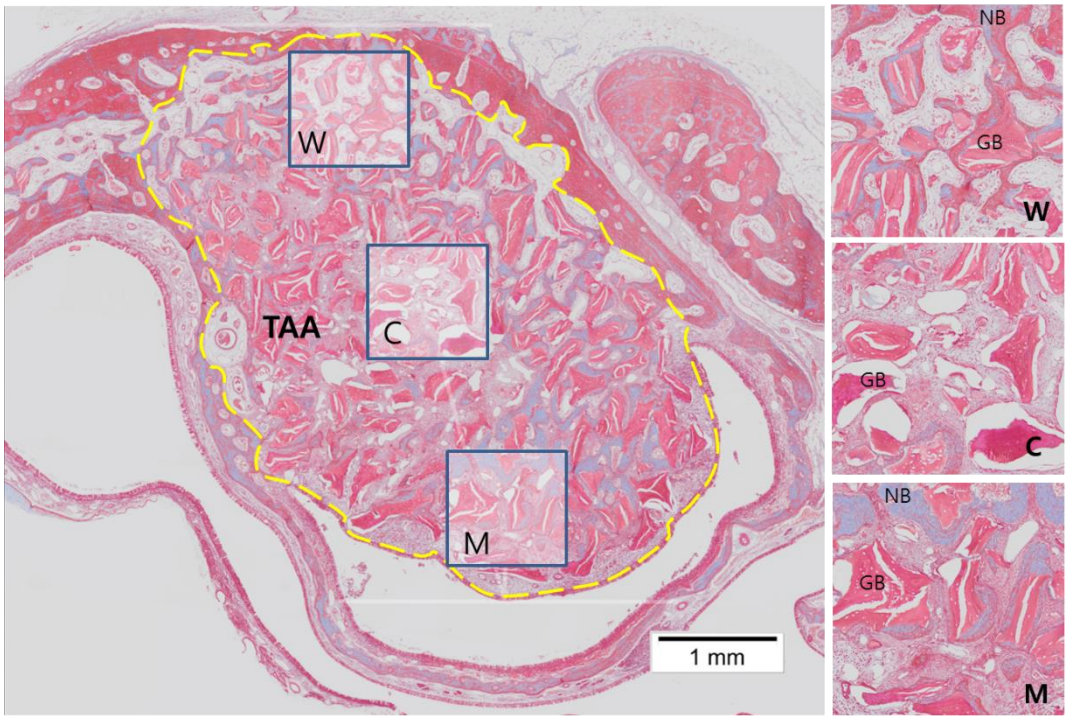

Figure 7. Masson's-trichrome-stained slide. Total augmented area (TAA) and three squares showing enlarge views in the window (W), center (C), Schneiderian membrane (M) regions. The particles stained light purple are grafted bone substitute material, and new bone is stained blue. NB, new bone; GB, grafted bone substitute.

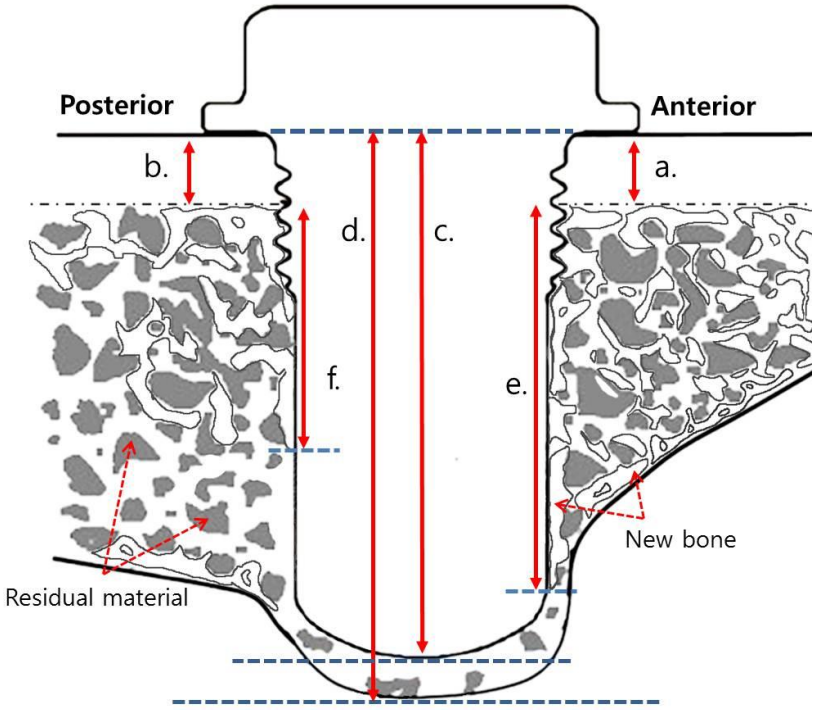

Figure 8. Linear measurements. (a) Cortical bone height (CBH), Anterior. (b) Cortical bone height, Posterior. (c) Protruding height (PH) (d) Augmented height (AH), (e) Osseointegration height (OH), Anterior. (f) Osseointeration height, Posterior.

7. Statistics

Data was analyzed using SPSS 23.0 (IBM Corp., Armonk, NY, USA). Mann-Whitney test was used for comparing all parameters between saline group and PTH group. 1-way ANOVA test was used for differences between NBA values of window, center and membrane regions within each group. The level of significance was set at $p<0.05$.

Ⅲ. Results

1. Clinical findings

Among a total of 40 maxillary sinuses of 20 rabbits, one maxillary sinus in the PTH group was excluded because of the failure of defect formation.

2. Radiographic analysis of femur : microCT

Micro-CT imaging was performed with the femur to investigate the systemic effect of PTH in osteoporosis-induced rabbits. The BMD and bone volume fraction (BV/TV) were higher in the PTH group than saline group, and the difference between the two groups was significant. **(Table 1) (Figure 9)** The cross-sectional images also showed that the trabecular bone was more in the PTH group. **(Figure 10)**

Table 1. Femur Micro CT (㎜³, Mean± SD)

	BMD	BV/TV	Tb.N	Tb.Th	Tb.Sp
Saline (n=10)	0.08±0.12	6.06±1.42	0.24±0.62	0.24±0.27	4.14±0.33
PTH (n=10)	0.12±0.30	10.77±4.79	0.40±1.32	0.26 ±0.46	3.98 ±0.65
	p=0.001*	p=0.007*	p=0.003*	p=0.631	p=0.218

BMD : Bone mineral density, BV/TV : Bone volume fraction, Tb.N : Trabecular number, Tb.Th : Trabecular thickness, Tb.Sp : Trabecular separation

* significant difference between two groups (Mann-Whitney test)

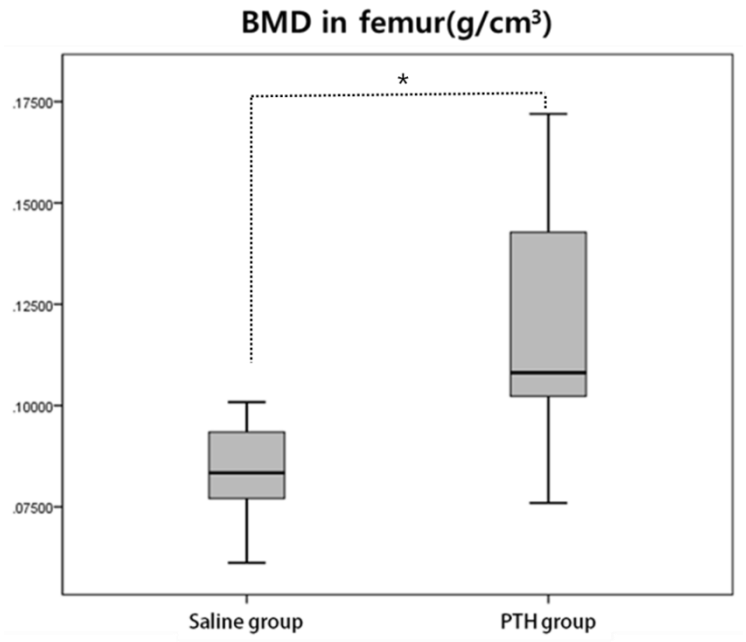

Figure 9. BMD analysis by microCT in femur was significantly higher in the PTH group.

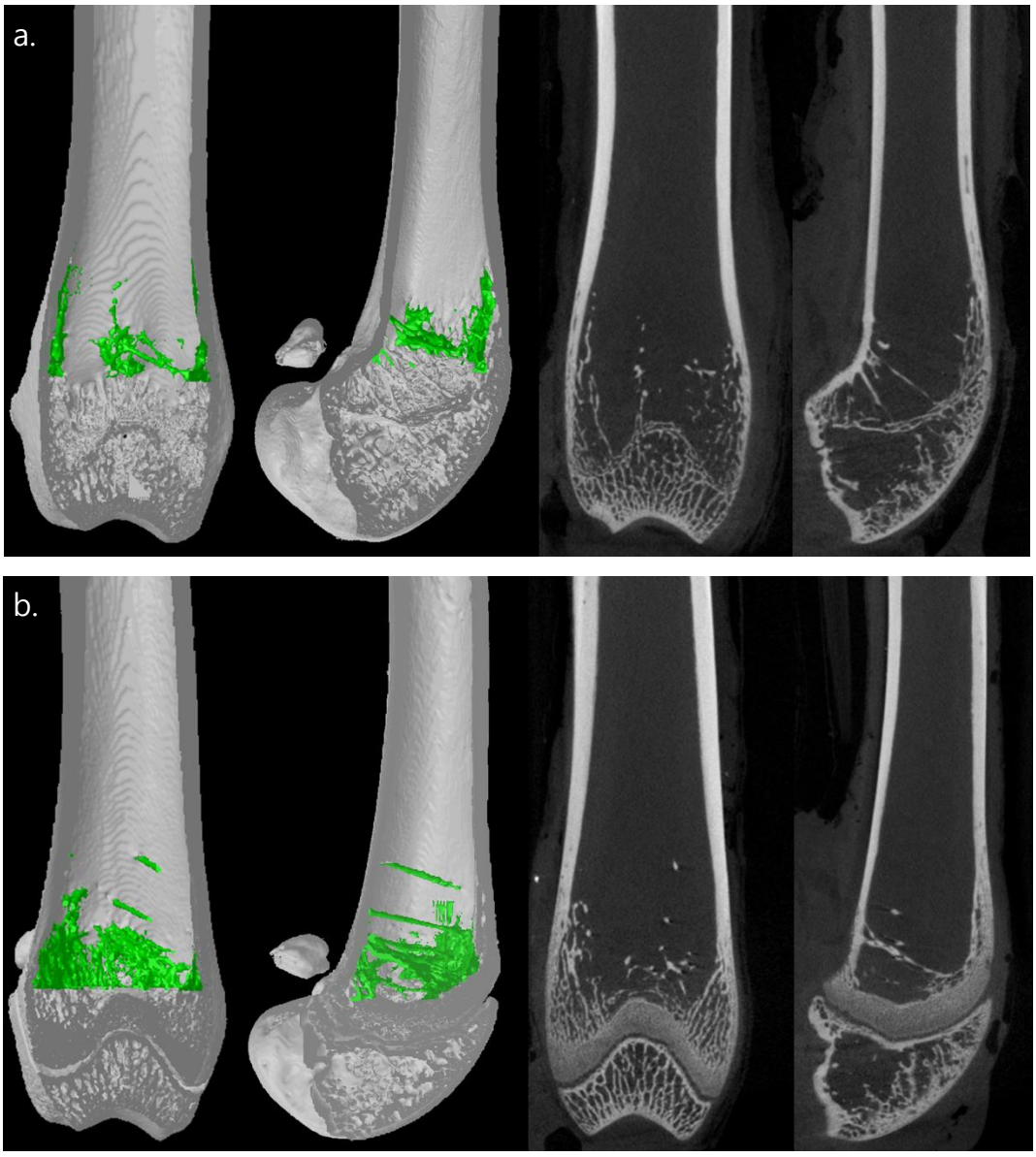

Figure 10. The trabecular pattern of distal femur by Micro CT. 3D coronal view, 3D sagittal view, 2D coronal view, 2D sagittal view images (from left to right). (a) saline group (b) PTH group. Each images belong to animal of the median value. The 3D images showed the trabecular bone mass of PTH group is more than saline group. 2D images showed the difference in bone formation between two groups around the growth plate.

3. Radiographic analysis of sinus : microCT

Micro-CT images of the bone grafted sinus were taken to measure the total bone volume (TBV), grafted bone volume (GBV), and new bone volume (NBV). TBV of saline group is 54.95±7.89, PTH group is 42.98±18.89, which were not significantly different between the two groups. **(Table 2) (Figure 11)**

Table 2. Sinus microCT (㎣, Mean± SD)

	TBV	GBV	NBV
Saline (n=20)	54.95±7.89	15.47±5.64	34.37±5.33
PTH (n=19)	42.98±18.89	12.38±12.02	29.45±6.04
	p=0.108	p=0.380	P=0.012

TBV : total bone volume, GBV : grafted bone substitute volume,
NBV : new bone volume.

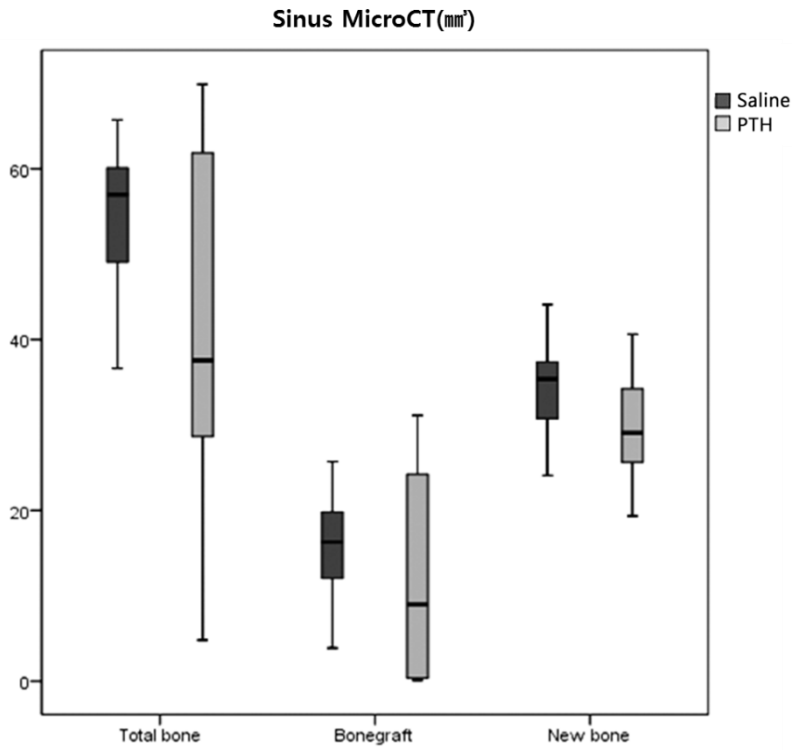

Figure 11. Sinus microCT result. There was no significant difference between PTH and saline group, and the difference between individuals was even greater in PTH group.

4. Histomorphometric analysis

The intraclass correlation coefficients (ICCs) of all the elements were measured to examine the interobserver reliability. The average of the ICCs was 0.92 (95%CI:0.88-0.95), indicating that the tissue measurements were reliable data. We used the average values of the measurements by the two observers.

All the area and length measurements showed no significant difference between the

two groups, and the variation between the subjects was even greater. **(Tables 3 and 4) (Figures 12, 13, and 14)** When area measurements of the detailed regions were compared, the new bone area was great in the order of the window, membrane, and center. A significant difference was found between the window and the center in both the saline group and the PTH group (Saline group p=0.003, PTH group p=0.005). The PTH group also showed a significant difference between the window region and the membrane region (p=0.008). None of the two groups showed a significant difference between the center and the membrane. **(Figure 13)**

Table 3. Histomorphometric analysis - Area measurements (%, Mean±SD)

	%NBA	%RMA	%CTA
Non-implant side			
Saline	15.91±3.76	37.95±4.90	46.14±3.18
PTH	13.67±4.30	37.35±3.92	48.98±5.35
Implant side			
Saline	19.07±2.91	33.92±2.44	47.01±3.27
PTH	17.51±2.69	33.26±1.11	49.23±2.56
Both			
Saline	17.01±3.74	36.54±4.58	46.45±3.16
PTH	15.09±4.16	35.84±3.73	49.07±4.44

NBA : new bone area, RMA : residual material area, CTA : connective tissue area, TAA : total augmented area.

%NBA = (NBA/TAA)*100, %RMA = (RMA/TAA)*100, %CTA = (CTA/TAA) *100

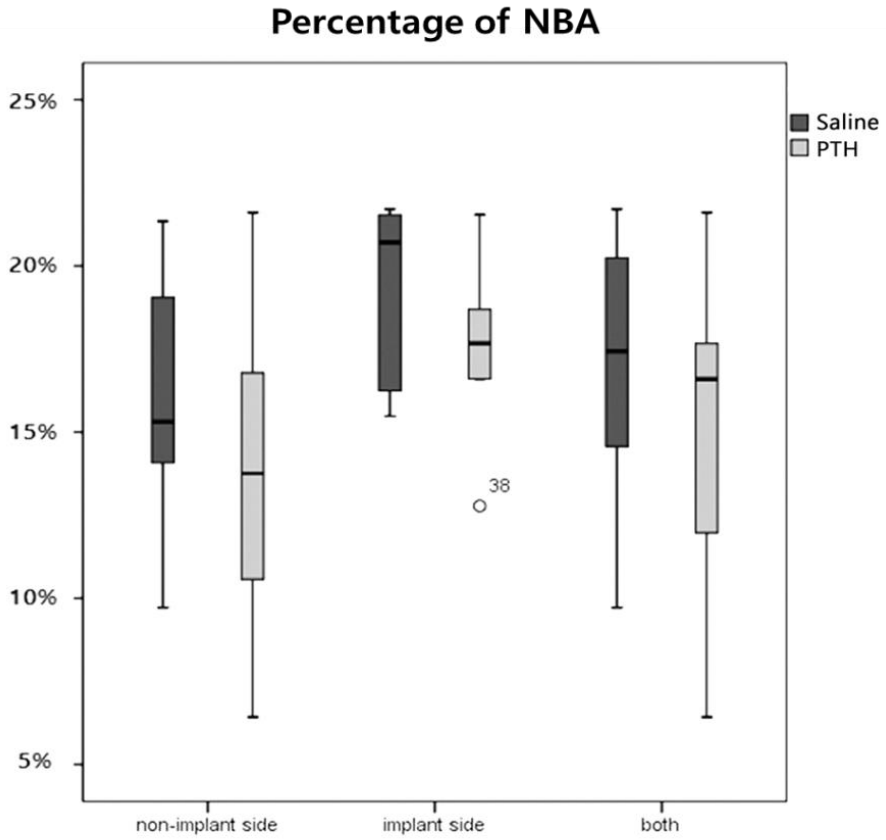

Figure 12. Histomorphometric analysis(Area measurements). %NBA=New bone area/Total augmented area *100%. There was no difference between the groups in all situations, but there seem to be many differences among individuals.

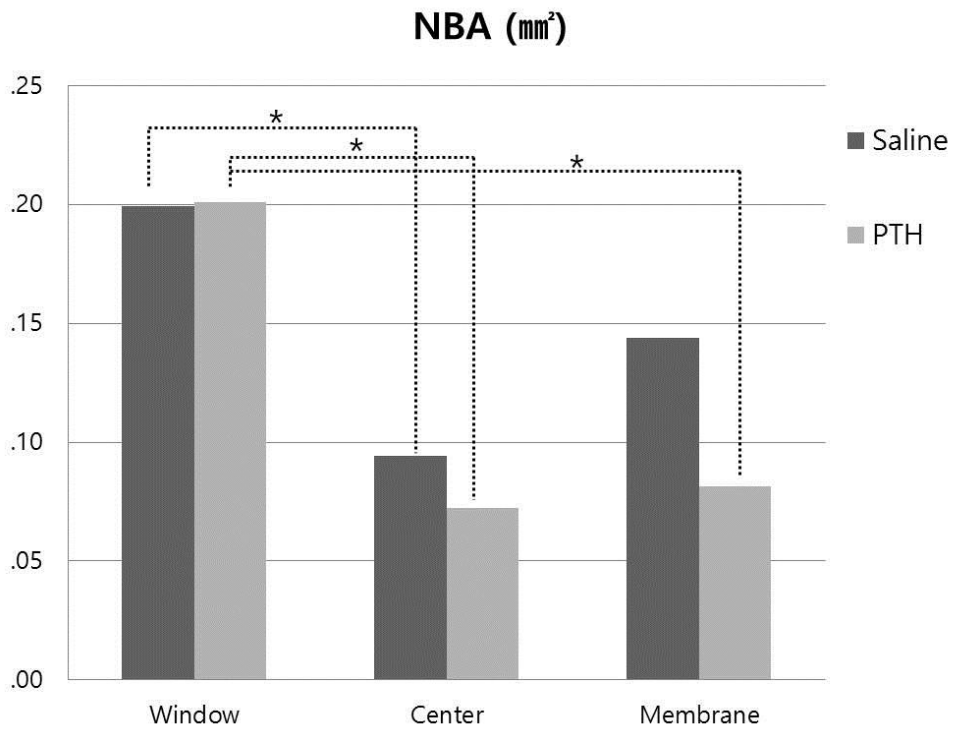

Figure 13. NBA within 1 ㎟ squares in the window, center, and Schneiderian membrane regions. New bone formation was significantly higher in the window region than in the center. Membrane region was slightly more than center, but there was no significant difference. 1-way ANOVA test was used, *P < 0.05.

Table 4. Histomorphometric analysis – linear measurements (㎟, Mean±SD)

	CBH(Ant.)	CBH(Pos.)	PH	AH	OH(Ant.)	OH(Pos.)
Saline	0.49±0.13	0.54±0.18	5.04±0.17	5.54±0.27	3.00±1.01	3.52±1.28
PTH	0.49±0.07	0.57±0.11	5.00±0.09	5.87±0.58	3.70±0.91	3.00±1.73

CBH : cortical bone height, OH : osseointegration height, PH : protruding height, AH : augmented height

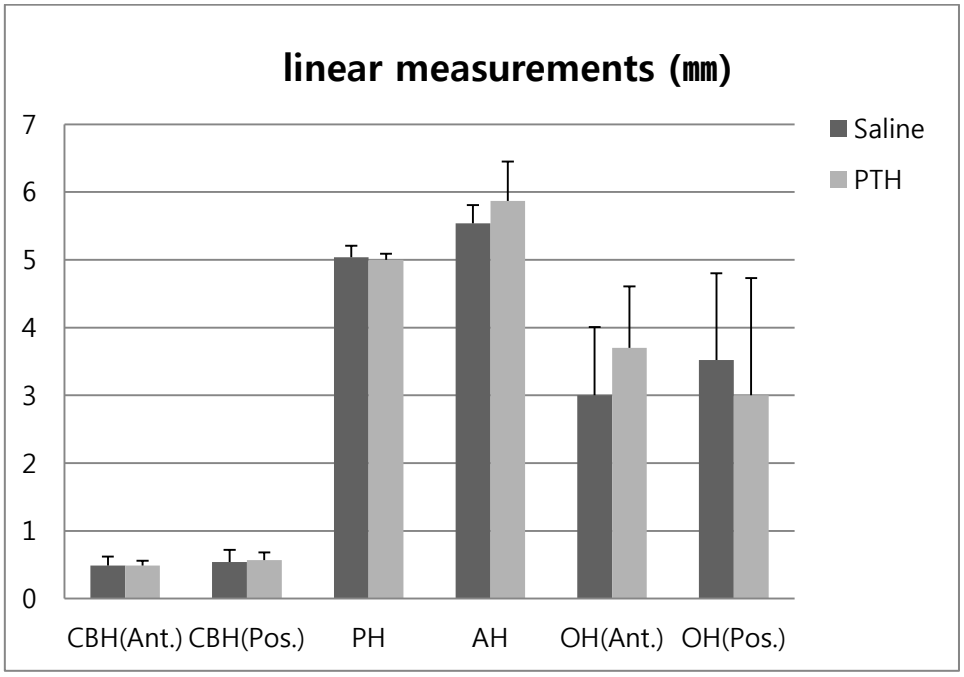

Figure 14. Histomorphometric analysis (linear measurements). CBH : cortical bone height, OH : osseointegration height, PH : protruding height, AH : augmented height There was no significant difference between groups in all parameters.

Ⅳ. Discussion

In the present study, the experiment was performed to investigate the effect of PTH on the bone graft to the maxillary sinus of osteoporosis-induced rabbits. To examine whether PTH has a systemic effect on osteoporosis-induced rabbits, micro-CT images were taken with the femur. The BMD value was found to be significantly higher in the PTH group than in the saline group, and the micro-CT images also showed that the trabecular bone was significantly increased in the PTH group. This suggests that PTH has an osteoporosis treatment effect systemically. However, neither the micro-CT images nor the histomorphometric analysis showed a difference in the new bone formation at the grafted sinus. This result implies that the PTH had no effect on the sinus grafted bone in the present study.

With regard to the reason why the PTH had an osteoporosis treatment effect on the femur but no bone formation effect on the sinus, the first possible cause may be the difference of the bone remodeling rate between the long bone and the maxillary bone. The appendicular bone and the oral facial bone have different embryological origin, and the main bone formation mechanism of long bones is endochondral ossification, while that of orofacial bones is intramembranous ossification. Akintoye et al.[45] conducted in 2006 in vivo and in vitro experiments and reported that human bone marrow stromal cells in different regions have different characteristics. Orofacial bone stromal cells showed a higher cell growth rate and a higher calcium and alkaline phosphatase concentration in

comparison with the iliac crest bone. In our experiment, the PTH was found to be more effective in the femur of which bone metabolism is slower than maxilla.

However, many of the animal studies, PTH was effective in not only long bones,[9,12,21] but also calvarial defect model[46-48] and the mandible.[49] Takahata et al.[50] reviewed that PTH (1-34) was effective on both endochondral and intramembranous bone healing. Therefore, the bone type may not be considered as a critical factor in our experiment.

The second consideration is the grafted site and material. Previous studies to investigate the effect of PTH on bone graft site were allograft or autograft at long bone, [51,52] spine fusion,[53] and calvarial defect.[46,48] Huh.et al. [42] is the only previous study investigating the effect of PTH on the sinus bone graft model. Considering that most of the previous studies on bone graft used autograft or allograft, the xenograft performed in the present study with rabbits is different from previous studies. In 2013, Kuroshima et al.[54] performed xenograft at the rat maxillary extraction sockets and administered PTH at 80μg/kg/day for 14 days, and reported that the bone volume measured by using the micro-CT images was increased in comparison with the control group but no significant difference was found between the graft materials (Aterocollagen, OraGRAFT, Bio-Oss). The study of Kuroshima et al.[54] has limitation in that the only measurement method was micro-CT.

The third consideration is the dose, administration frequency, and duration. In previous PTH studies to rabbits, the dose was various as 6[55], 8[56], 10[30], 25[49], 30[38], and 40[57]μg/kg/day,

and the appropriate range of dose for rabbits was considered to be 10 to 40㎍/㎏/day.[58] The administration frequency found in previous studies included 3 days or 5 days weekly, daily injection, or once in 4 to 25 weeks. The dose and duration are even more various if those applied to experiments involving other animals are considered. We reviewed the doses applied to previous studies and found that PTH helped bone formation in most of the studies except at an extremely low dose and the effect did not seem to be dose-dependent over a certain dose value.[52,59,60]

In our experiment, PTH was administered at 10 ㎍/㎏/day for five weeks (1 week before sinus surgery, 4 weeks after sinus surgery) to investigate the effect at a minimum dose during a minimum period. In the study by Huh. et al. [42] where bone augmentation was performed in the healthy rabbit sinus, PTH subcutaneous injection was performed at a dose of 10 ㎍/㎏ for two weeks and for four weeks and the comparison showed that more bone formation was found in the four-week administration group than in the two-week administration group. However, no significant difference was found between the PTH group and the saline group. We consider that the homeostasis of the other bone formation factors was maintained in healthy animals even after the PTH administration. In our experiment, the same dose and administration method were used to ovariectomized female rabbits. In the present study, PTH was pretreated from one week before the sinus surgery and then administered for four postoperative weeks. Studies are required to investigate how long PTH should be administered preoperatively or postoperatively to acquire the effect.

In clinical studies of PTH, Hodsman et al.[61] in 1992 had daily subcutaneous injection of 800 IU (50μg) PTH (1-34) for four weeks with 20 osteoporosis patients, and reported that serum alkaline phosphatase, osteocalcin, and carboxy-terminal extension peptide of procollagen were significantly increased on the 28th day. In 2014, Kim et al.[29] performed daily subcutaneous injection of 20μg PTH (1-34) to bisphosphonate-related osteonecrosis of the jaw (BRONJ) patients for six months, measured the osteocalcin and CTX (c-telopeptide of type I collagen) on every one, three, and six months, and reported that measurement value started to increase from the first month and showed a significant difference on the third month and the sixth month.

The fourth consideration is the characteristics of the animals. Rabbits were selected as experimental animals in the present study due to the sinus model. The rabbit sinus is a good model for reproducing sinus lift and bone graft. However, the metabolic rate of the rabbit sinus is three to four times higher than that of humans, and bone healing in rabbits is rapidly completed within a few weeks.[62] No difference was found in the present study between the groups probably because of the high metabolic rate of rabbit sinus. The bone remodeling and bone formation factors may need to be investigated at a protein or cell level.

Reviewing all considerations, we speculated as follows the reasons why PTH, which was found to be effective in other studies, was not effective in our experiment. In various previous experimental models, including calvarial defect, extraction socket, distraction

osteogenesis, spine fusion, and bone fracture healing models, the normal body structure was damaged and subsequently, PTH was involved in the homeostasis of the body to repair the damage. In contrast, since the sinus model of the present study was established by adding abnormal augmentation to normal tissue, the PTH might not have shown an effect. Furthermore, maxillary sinus lift area is a good environment for bone formation, so PTH in rabbit sinus might not be effective.

If a better effect was found in the PTH group in comparison with the saline group and the difference was significant, further studies would be required to identify the causes. However, the experimental data of the present study showed no significant difference between the groups, and the difference between individuals was even greater. Therefore, it can be concluded that PTH may not effective on sinus bone graft, and no further study is necessary in this regard. Future studies may need to be conducted on various drug substances that may facilitate healing of sinus bone graft.

Ⅴ. Conclusions

Intermittent PTH might not promote new bone formation in the augmented maxillary sinus of ovariectomized rabbits

REFERENCES

1. Wallace, S.S., Froum, S.J. & Tarnow, D.P. (1996) Histologic evaluation of a sinus elevation procedure: a clinical report. *Int J Periodontics Restorative Dent* 16: 46-51.
2. Hurzeler, M.B., Kirsch, A., Ackermann, K.L. & Quinones, C.R. (1996) Reconstruction of the severely resorbed maxilla with dental implants in the augmented maxillary sinus: a 5-year clinical investigation. *Int J Oral Maxillofac Implants* 11: 466-475.
3. Avera, S.P., Stampley, W.A. & McAllister, B.S. (1997) Histologic and clinical observations of resorbable and nonresorbable barrier membranes used in maxillary sinus graft containment. *Int J Oral Maxillofac Implants* 12: 88-94.
4. Fugazzotto, P.A. (1994) Maxillary sinus grafting with and without simultaneous implant placement: technical considerations and case reports. *Int J Periodontics Restorative Dent* 14: 544-551.
5. Smiler, D.G. (1997) The sinus lift graft: basic technique and variations. *Pract Periodontics Aesthet Dent* 9: 885-893; quiz 895.
6. Blomqvist, J.E., Alberius, P., Isaksson, S., Linde, A. & Hansson, B.G. (1996) Factors in implant integration failure after bone grafting: an osteometric and endocrinologic matched analysis. *Int J Oral Maxillofac Surg* 25: 63-68.
7. Li, M., Liang, H., Shen, Y. & Wronski, T.J. (1999) Parathyroid hormone stimulates cancellous bone formation at skeletal sites regardless of marrow composition in ovariectomized rats. *Bone* 24: 95-100.
8. Watson, P.H., Fraher, L.J., Kisiel, M., DeSousa, D., Hendy, G. & Hodsman, A.B. (1999) Enhanced osteoblast development after continuous infusion of hPTH(1-84) in the rat. *Bone* 24: 89-94.
9. Jahng, J.S. & Kim, H.W. (2000) Effect of intermittent administration of parathyroid hormone on fracture healing in ovariectomized rats. *Orthopedics* 23: 1089-1094.
10. Nakajima, A., Shimoji, N., Shiomi, K., Shimizu, S., Moriya, H., Einhorn, T.A. & Yamazaki, M. (2002) Mechanisms for the enhancement of fracture healing in

rats treated with intermittent low-dose human parathyroid hormone (1-34). *J Bone Miner Res* 17: 2038-2047.

11. Dobnig, H. & Turner, R.T. (1995) Evidence that intermittent treatment with parathyroid hormone increases bone formation in adult rats by activation of bone lining cells. *Endocrinology* 136: 3632-3638.
12. Kakar, S., Einhorn, T.A., Vora, S., Miara, L.J., Hon, G., Wigner, N.A., Toben, D., Jacobsen, K.A., Al-Sebaei, M.O., Song, M., Trackman, P.C., Morgan, E.F., Gerstenfeld, L.C. & Barnes, G.L. (2007) Enhanced chondrogenesis and Wnt signaling in PTH-treated fractures. *J Bone Miner Res* 22: 1903-1912.
13. Daugaard, H. (2011) The influence of parathyroid hormone treatment on implant fixation. *Dan Med Bull* 58: B4317.
14. Neer, R.M., Arnaud, C.D., Zanchetta, J.R., Prince, R., Gaich, G.A., Reginster, J.Y., Hodsman, A.B., Eriksen, E.F., Ish-Shalom, S., Genant, H.K., Wang, O. & Mitlak, B.H. (2001) Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med* 344: 1434-1441.
15. Orwoll, E.S., Scheele, W.H., Paul, S., Adami, S., Syversen, U., Diez-Perez, A., Kaufman, J.M., Clancy, A.D. & Gaich, G.A. (2003) The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. *J Bone Miner Res* 18: 9-17.
16. Lane, N.E., Sanchez, S., Modin, G.W., Genant, H.K., Pierini, E. & Arnaud, C.D. (1998) Parathyroid hormone treatment can reverse corticosteroid-induced osteoporosis. Results of a randomized controlled clinical trial. *J Clin Invest* 102: 1627-1633.
17. Body, J.J., Gaich, G.A., Scheele, W.H., Kulkarni, P.M., Miller, P.D., Peretz, A., Dore, R.K., Correa-Rotter, R., Papaioannou, A., Cumming, D.C. & Hodsman, A.B. (2002) A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1-34)] with alendronate in postmenopausal women with osteoporosis. *J Clin Endocrinol Metab* 87: 4528-4535.
18. Hock, J.M., Gera, I., Fonseca, J. & Raisz, L.G. (1988) Human parathyroid

hormone-(1-34) increases bone mass in ovariectomized and orchidectomized rats. *Endocrinology* 122: 2899-2904.

19. Shen, V., Birchman, R., Liang, X.G., Wu, D.D., Dempster, D.W. & Lindsay, R. (1998) Accretion of bone mass and strength with parathyroid hormone prior to the onset of estrogen deficiency can provide temporary beneficial effects in skeletally mature rats. *J Bone Miner Res* 13: 883-890.
20. Liu, C.C. & Kalu, D.N. (1990) Human parathyroid hormone-(1-34) prevents bone loss and augments bone formation in sexually mature ovariectomized rats. *J Bone Miner Res* 5: 973-982.
21. Kim, H.W. & Jahng, J.S. (1999) Effect of intermittent administration of parathyroid hormone on fracture healing in ovariectomized rats. *Iowa Orthop J* 19: 71-77.
22. Storm, T., Thamsborg, G., Steiniche, T., Genant, H.K. & Sorensen, O.H. (1990) Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. *N Engl J Med* 322: 1265-1271.
23. Chandra, A., Lin, T., Tribble, M.B., Zhu, J., Altman, A.R., Tseng, W.J., Zhang, Y., Akintoye, S.O., Cengel, K., Liu, X.S. & Qin, L. (2014) PTH1-34 alleviates radiotherapy-induced local bone loss by improving osteoblast and osteocyte survival. *Bone* 67: 33-40.
24. Marques, M.R., da Silva, M.A., Manzi, F.R., Cesar-Neto, J.B., Nociti, F.H., Jr. & Barros, S.P. (2005) Effect of intermittent PTH administration in the periodontitis-associated bone loss in ovariectomized rats. *Arch Oral Biol* 50: 421-429.
25. Miller, S.C., Hunziker, J., Mecham, M. & Wronski, T.J. (1997) Intermittent parathyroid hormone administration stimulates bone formation in the mandibles of aged ovariectomized rats. *J Dent Res* 76: 1471-1476.
26. Bashutski, J.D., Eber, R.M., Kinney, J.S., Benavides, E., Maitra, S., Braun, T.M., Giannobile, W.V. & McCauley, L.K. (2010) Teriparatide and osseous regeneration in the oral cavity. *N Engl J Med* 363: 2396-2405.
27. Doh, R.M., Park, H.J., Rhee, Y., Kim, H.S., Huh, J. & Park, W. (2015) Teriparatide

therapy for bisphosphonate-related osteonecrosis of the jaw associated with dental implants. *Implant Dent* 24: 222-226.

28. Kuroshima, S., Entezami, P., McCauley, L.K. & Yamashita, J. (2014) Early effects of parathyroid hormone on bisphosphonate/steroid-associated compromised osseous wound healing. *Osteoporos Int* 25: 1141-1150.
29. Kim, K.M., Park, W., Oh, S.Y., Kim, H.J., Nam, W., Lim, S.K., Rhee, Y. & Cha, I.H. (2014) Distinctive role of 6-month teriparatide treatment on intractable bisphosphonate-related osteonecrosis of the jaw. *Osteoporos Int* 25: 1625-1632.
30. Almagro, M.I., Roman-Blas, J.A., Bellido, M., Castaneda, S., Cortez, R. & Herrero-Beaumont, G. (2013) PTH [1-34] enhances bone response around titanium implants in a rabbit model of osteoporosis. *Clin Oral Implants Res* 24: 1027-1034.
31. Fahlgren, A., Yang, X., Ciani, C., Ryan, J.A., Kelly, N., Ko, F.C., van der Meulen, M.C. & Bostrom, M.P. (2013) The effects of PTH, loading and surgical insult on cancellous bone at the bone-implant interface in the rabbit. *Bone* 52: 718-724.
32. Heo, H.A., Park, S.H., Jeon, Y.S. & Pyo, S.W. (2016) Enhancing Effect of Intermittent Parathyroid Hormone Administration on Bone Formation After Titanium Implant Placement in an Ovariectomized Rat Maxilla. *Implant Dent* 25: 227-231.
33. Javed, F., Al Amri, M.D., Kellesarian, S.V., Al-Kheraif, A.A., Vohra, F., Calvo-Guirado, J.L., Malmstrom, H. & Romanos, G.E. (2016) Efficacy of parathyroid hormone supplementation on the osseointegration of implants: a systematic review. *Clin Oral Investig* 20: 649-658.
34. Kamo, K., Miyakoshi, N., Kasukawa, Y., Nozaka, K., Sasaki, H. & Shimada, Y. (2010) Intermittent weekly administration of human parathyroid hormone (1-34) improves bone-hydroxyapatite block bonding in ovariectomized rats. *J Bone Miner Metab* 28: 634-640.
35. Ohkawa, Y., Tokunaga, K. & Endo, N. (2008) Intermittent administration of human parathyroid hormone (1-34) increases new bone formation on the interface of hydroxyapatitecoated titanium rods implanted into ovariectomized

rat femora. *J Orthop Sci* 13: 533-542.

36. Oki, Y., Doi, K., Makihara, Y., Kubo, T., Oue, H. & Tsuga, K. (2016) Intermittent administration of parathyroid hormone enhances primary stability of dental implants in a bone-reduced rabbit model. *J Oral Sci* 58: 241-246.
37. Park, S., Heo, H.A., Kim, K.W., Min, J.S. & Pyo, S.W. (2016) Intermittent Parathyroid Hormone Improves Bone Formation Around Titanium Implants in Osteoporotic Rat Maxillae. *Int J Oral Maxillofac Implants*; doi:10.11607/jomi.5037.
38. Shirota, T., Tashiro, M., Ohno, K. & Yamaguchi, A. (2003) Effect of intermittent parathyroid hormone (1-34) treatment on the bone response after placement of titanium implants into the tibia of ovariectomized rats. *J Oral Maxillofac Surg* 61: 471-480.
39. Skripitz, R., Johansson, H.R., Ulrich, S.D., Werner, A. & Aspenberg, P. (2009) Effect of alendronate and intermittent parathyroid hormone on implant fixation in ovariectomized rats. *J Orthop Sci* 14: 138-143.
40. Tao, Z.S., Zhou, W.S., Qiang, Z., Tu, K.K., Huang, Z.L., Xu, H.M., Sun, T., Lv, Y.X., Cui, W. & Yang, L. (2016) Intermittent administration of human parathyroid hormone (1-34) increases fixation of strontium-doped hydroxyapatite coating titanium implants via electrochemical deposition in ovariectomized rat femur. *J Biomater Appl* 30: 952-960.
41. Tao, Z.S., Zhou, W.S., Tu, K.K., Huang, Z.L., Zhou, Q., Sun, T., Lv, Y.X., Cui, W. & Yang, L. (2015) The effects of combined human parathyroid hormone (1-34) and simvastatin treatment on osseous integration of hydroxyapatite-coated titanium implants in the femur of ovariectomized rats. *Injury* 46: 2164-2169.
42. Huh, J., Jung, U.W., Park, K.M., Kim, H.S., Kim, K.D. & Park, W. (2017) Parathyroid Hormone (1-34) Might Not Improve Early Bone Healing after Sinus Augmentation in Healthy Rabbits. *Biomed Res Int* 2017: 6087676.
43. Choi, Y., Yun, J.H., Kim, C.S., Choi, S.H., Chai, J.K. & Jung, U.W. (2012) Sinus augmentation using absorbable collagen sponge loaded with Escherichia coli-expressed recombinant human bone morphogenetic protein 2 in a standardized rabbit sinus model: a radiographic and histologic analysis. *Clin*

Oral Implants Res 23: 682-689.

44. Jung, U.W., Unursaikhan, O., Park, J.Y., Lee, J.S., Otgonbold, J. & Choi, S.H. (2015) Tenting effect of the elevated sinus membrane over an implant with adjunctive use of a hydroxyapatite-powdered collagen membrane in rabbits. *Clin Oral Implants Res* 26: 663-670.
45. Akintoye, S.O., Lam, T., Shi, S., Brahim, J., Collins, M.T. & Robey, P.G. (2006) Skeletal site-specific characterization of orofacial and iliac crest human bone marrow stromal cells in same individuals. *Bone* 38: 758-768.
46. Sheyn, D., Cohn Yakubovich, D., Kallai, I., Su, S., Da, X., Pelled, G., Tawackoli, W., Cook-Weins, G., Schwarz, E.M., Gazit, D. & Gazit, Z. (2013) PTH promotes allograft integration in a calvarial bone defect. *Mol Pharm* 10: 4462-4471.
47. Andreassen, T.T. & Cacciafesta, V. (2004) Intermittent parathyroid hormone treatment enhances guided bone regeneration in rat calvarial bone defects. *J Craniofac Surg* 15: 424-427; discussion 428-429.
48. dos Santos, R.A., Ferreira, M.S., Mafra, C.E., Holzhausen, M., de Lima, L.A., Mendes Pannuti, C. & Cesar Neto, J.B. (2016) Synthetic Parathyroid Hormone May Augment Bone Volume in Autogenous Grafts: A Study in Rats. *J Periodontol* 87: 66-73.
49. Tang, Z.L., Zhang, W.J., Wang, D.X., Chen, J.M., Ma, H. & Wu, D.R. (2014) An experimental study addressing the promotion of mandibular defect repair through the intermittent subcutaneous injection of parathyroid hormone. *J Oral Maxillofac Surg* 72: 419-430.
50. Takahata, M., Awad, H.A., O'Keefe, R.J., Bukata, S.V. & Schwarz, E.M. (2012) Endogenous tissue engineering: PTH therapy for skeletal repair. *Cell Tissue Res* 347: 545-552.
51. Daugaard, H., Elmengaard, B., Andreassen, T.T., Baas, J., Bechtold, J.E. & Soballe, K. (2011) The combined effect of parathyroid hormone and bone graft on implant fixation. *J Bone Joint Surg Br* 93: 131-139.
52. Takahata, M., Schwarz, E.M., Chen, T., O'Keefe, R.J. & Awad, H.A. (2012) Delayed short-course treatment with teriparatide (PTH(1-34)) improves femoral allograft healing by enhancing intramembranous bone formation at the graft-

host junction. *J Bone Miner Res* 27: 26-37.

53. Abe, Y., Takahata, M., Ito, M., Irie, K., Abumi, K. & Minami, A. (2007) Enhancement of graft bone healing by intermittent administration of human parathyroid hormone (1-34) in a rat spinal arthrodesis model. *Bone* 41: 775-785.
54. Kuroshima, S., Al-Salihi, Z. & Yamashita, J. (2013) Parathyroid hormone related to bone regeneration in grafted and nongrafted tooth extraction sockets in rats. *Implant Dent* 22: 71-76.
55. Corsini, M.S., Faraco, F.N., Castro, A.A., Onuma, T., Sendyk, W.R. & Shibli, J.A. (2008) Effect of systemic intermittent administration of human parathyroid hormone (rhPTH[1-34]) on the resistance to reverse torque in rabbit tibiae. *J Oral Implantol* 34: 298-302.
56. Kimura, S., Saito, M., Kida, Y., Seki, A., Isaka, Y. & Marumo, K. (2016) Effects of raloxifene and alendronate on non-enzymatic collagen cross-links and bone strength in ovariectomized rabbits in sequential treatments after daily human parathyroid hormone (1-34) administration. *Osteoporos Int*; doi:10.1007/s00198-016-3812-3.
57. Bellido, M., Lugo, L., Castaneda, S., Roman-Blas, J.A., Rufian-Henares, J.A., Navarro-Alarcon, M., Largo, R. & Herrero-Beaumont, G. (2010) PTH increases jaw mineral density in a rabbit model of osteoporosis. *J Dent Res* 89: 360-365.
58. Hirano, T., Burr, D.B., Turner, C.H., Sato, M., Cain, R.L. & Hock, J.M. (1999) Anabolic effects of human biosynthetic parathyroid hormone fragment (1-34), LY333334, on remodeling and mechanical properties of cortical bone in rabbits. *J Bone Miner Res* 14: 536-545.
59. Gabet, Y., Muller, R., Levy, J., Dimarchi, R., Chorev, M., Bab, I. & Kohavi, D. (2006) Parathyroid hormone 1-34 enhances titanium implant anchorage in low-density trabecular bone: a correlative micro-computed tomographic and biomechanical analysis. *Bone* 39: 276-282.
60. Jerome, C.P. (1994) Anabolic effect of high doses of human parathyroid hormone (1-38) in mature intact female rats. *J Bone Miner Res* 9: 933-942.
61. Hodsman, A.B., Fraher, L.J., Ostbye, T., Adachi, J.D. & Steer, B.M. (1993) An

evaluation of several biochemical markers for bone formation and resorption in a protocol utilizing cyclical parathyroid hormone and calcitonin therapy for osteoporosis. *J Clin Invest* 91: 1138-1148.

62. Roberts, W.E., Turley, P.K., Brezniak, N. & Fielder, P.J. (1987) Implants: Bone physiology and metabolism. *Cda j* 15: 54-61.

국문 요약

난소절제된 토끼 상악동 골이식 모델에서 부갑상선 호르몬 (1-34) 투여가 골 치유에 미치는 영향

< 지도교수 박원서 >

연세대학교 대학원 치의학과

담 추 금

연구 배경 및 목적 : 상악동 증강술 시 골 이식재가 골 형성이 될 때까지 상당기간 기다려야 한다는 단점이 있다. 우리는 이 기간을 줄일 수 있을지에 대해 연구를 하기 위해 골다공증 치료제 중 부갑상선호르몬 [Teriparatide , PTH (1-34), 이하 PTH]에 주목했다. 현재 쓰이고 있는 골다공증 치료제의 대부분은 골 흡수 억제제로 파골세포의 활성을 저하시켜 골밀도를 증가시키는

반면, PTH 주사제는 간헐적인 투여 시 조골세포의 활성을 증가시켜 골형성을 촉진한다.

PTH가 골밀도를 증가시키고 골치유에 도움을 준다는 선행 연구들을 기반으로 하여, 건강한 토끼에서 상악동 증강술을 시행 한 후 PTH의 효과를 보기 위한 선행 연구가 있었고, 그 결과 신생골 형성을 촉진 시키지 않는다는 결론을 얻었다. 때문에 본 연구에서는 난소 절제 후 골다공증이 유발된 토끼에서 실험을 시행했다. 본 연구의 목적은 난소절제술을 시행한 토끼에서 임플란트를 동반한 (또는 동반하지 않은) 상악동 증강술 시 PTH가 미치는 영향을 알아보고자 한다.

재료 및 방법 : 20마리 암컷 토끼에 난소절제술을 시행하고, PTH군 (n=10)과 Saline군 (n=10)에 따라 PTH 10 μg/kg, 혹은 동량의 생리식염수를 상악동 수술 전 1주, 수술 후 4주 동안 주 5회 피하 주사하였다. 20마리 토끼의 총 40개의 상악동 중 각 군당 13개의 상악동에 Bio-oss®를 이식하고 7개의 상악동에는 골이식과 임플란트를 동시에 시행했다. 술 후 4주째 희생했다.

PTH가 전신적으로 효과가 있었는지 보기 위해 microCT를 이용하여 오른쪽 대퇴골의 골밀도를 측정했으며, 상악동 수술 부위는 방사선학적 및 조직계측학적 분석을 시행하였다. 통계는 Mann-Whitney 검정을 사용했다.

결과 : 대퇴골에서는 BMD가 증가되었으나, 상악동 증강술을 시행한 부위에서는 방사선학적 계측 및 조직 계측의 모든 항목에서 PTH군과 Saline군 간에 골치유에 차이가 없었고, 오히려 개체간의 차이가 더 컸다.

결론 : 난소절제술을 시행하여 골다공증이 유발된 토끼에서 상악동 증강술 후 부갑상선호르몬 (1-34)의 간헐적 투여는 초기 치유기간 내에서 신생골 형성을 촉진하지 않는다.

핵심되는 말: teraparatied, 부갑상선 호르몬, 상악동 증강술, 토끼 상악동 모델, 난소절제술