# Bone response to three different dental implant surfaces with *Escherichia coli*-derived recombinant human bone morphogenetic protein-2 in a rabbit model

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# Bone response of three different dental implant surfaces with *Escherichia coli*-derived recombinant human bone morphogenetic protein-2 in a rabbit model

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저자 씀

# Table of Contents

# List of Figures



# List of Tables

## Abstract

### Bone response to three different dental implant surfaces with *Escherichia coli*-derived recombinant human bone morphogenetic protein-2 in a rabbit model

**Purpose**: The objective of this study was to analyze orthotropic bone formation/remodeling of three different dental implant surfaces with/without recombinant human bone morphogenetic protein-2 derived from *Escherichia coli* (ErhBMP-2) in a rabbit model.

**Materials and Methods**: Resorbable blasting media (RBM), sandblasted large grit and acid-etched (SLA), and Mg-incorporated oxidized (MgO) surfaces were coated with ErhBMP-2 (1.5 mg/mL). The implants were placed into the proximal tibia in six New Zealand White rabbits. Each rabbit received six different implants (three coated with ErhBMP-2 in one tibia and three uncoated implants in the other tibia) and the sites were closed submerging the implants. The animals received alizarin (2-week), calcein (4-week), and tetracycline (6-week) fluorescent bone markers; they were euthanized at 8-week for histomorphometric analysis.

**Results**: Amount of coated ErhBMP-2 was 9.6±0.4 μg/MgO, 14.5±0.6 μg/RBM, and 29.9±3.8 μg/SLA per implant. Clinical healing was uneventful. Considering the entire

implant, mean bone-implant contact (±SD) for the ErhBMP-2/RBM (35.4±5.1%) and ErhBMP-2/MgO (33.4±13.2%) implants was significantly greater compared with RBM (23.6±6.2%) and MgO (24.9±2.7%) implants ($p<0.05$). However, ErhBMP-2/SLA implants (19.1±7.2%) showed slightly lower bone-implant contact compared with SLA implants (23.4±3.8%; $p > .05$). Considering mean bone-implant contact in cortical bone and bone area within the threads, there were no significant differences between ErhBMP-2 coated and uncoated RBM and MgO implants. ErhBMP-2/SLA implants (32.9±7.8%) showed lower bone-implant contact than all other implant variations (range 39.9±18.1% - 51.3±9.2%; $p < .05$). Similarly there were no remarkable differences in new bone area with minor differences between implants.

**Conclusions**: Within the limits of this study, absorbed ErhBMP-2 dose varies with implant surface characteristics in turn influencing local bone formation/remodeling.

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**Key Words**: bone morphogenetic protein; dental implant; histomorphometry; fluorochrome sequential labeling

# Bone response to three different dental implant surfaces with *Escherichia coli*-derived recombinant human bone morphogenetic protein-2 in a rabbit model

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## I. Introduction

Pure titanium cannot promote new bone formation on its surface at the early stage of osseointegration. Therefore, numerous attempts have been made to enhance osseointegration and reduce the healing time, by improving implant biocompatibility and modifying the surface characteristics mechanically, chemically, and/or biologically using methods such as blasting, plasma spraying, blasting and etching, micro-arc oxidation, and growth factor application.[1-5]

Several growth factors, such as bone morphogenetic proteins (BMPs), insulin-like growth factor-1, and basic fibroblast growth factor have been shown to improve osteoblast differentiation and matrix mineralization. Among them, BMPs are powerful inducers of osteoblast differentiation and bone formation.[6] More than 20 different isoforms of BMP have been described, but BMP-2 and BMP-7 are thought to play the most important roles in the skeletal system.[6,7]

The results of recent studies suggest that BMPs have an affinity to titanium, and hence titanium implants have been considered as potential carrier for BMPs.[8-11] Several studies have evaluated the possibility of developing a load-bearing implant that could deliver recombinant human BMP-2 (rhBMP-2) for oral and maxillofacial reconstruction. Hall et al.[12] reported that rhBMP-2 coated titanium porous oxide (TPO) implants exhibited osteoinductive effects in a rat ectopic model, including bone contact to the implant surface. Wikesjö et al.[13,15] showed that in a critical-size, supra-alveolar, peri-implant defect model, rhBMP-2 coated implants induced new bone formation and osseointegration following an 8-week healing period. Similar accelerated local bone formation has been observed for implants coated with rhBMP-2 placed into type II bone in dogs and type IV bone in non-human primates.[14,15] However, Leknes et al.[16] and Wikesjö et al.[10] reported that high concentrations/doses of rhBMP-2 induced undesirable implant displacement. They concluded that the application of rhBMP-2 at appropriate concentrations/doses may induce clinically

relevant local bone formation including vertical augmentation of the alveolar ridge and osseointegration, whereas higher concentrations/doses were associated with undesirable effects.

Previously, most rhBMP-2 is obtained from mammalian cells, such as Chinese hamster ovary (CHO) cells.[17,18] However, the low yield (ng/ml) of rhBMP-2 production in well-established eukaryotic protein expression system has been considered a major problem for clinical applications. One possible method of solving this problem is to use rhBMP-2 derived from *Escherichia coli* (ErhBMP-2), which can be produced at a low cost.[19,20] Bessho et al.[20] demonstrated that the bone-inducing ability of ErhBMP-2 was similar to that of CHO-cell-derived rhBMP-2 (CrhBMP-2).

While a few studies have shown improved bone responses of CrhBMP-2-coated TPO implants, little attention has been paid to ErhBMP-2-coated surface-modified implants.

Therefore, the purpose of this study was to analyze bone formation/remodeling of three different dental implant surfaces with/without ErhBMP-2 using a rabbit model *in vitro and in vivo*.

# Ⅱ. Materials & Methods

## 1. *In Vitro* Study

### 1.1. Preparation of the ErhBMP-2 coated Implants

Dental implants with three different surface characteristics were used: a resorbable blasting media (RBM) implant (3.5 mm in diameter and 8.5 mm long; GS III$^{TM}$, Osstem Implants, Busan, Korea), sandblasted large-grit and acid-etched (SLA) implant (3.5 mm in diameter and 8.5 mm long; TS III$^{TM}$, Osstem Implants), and Mg-incorporated oxidized (MgO) implant (3.3 mm in diameter and 8.0 mm long; Shinhung Implant M$^{TM}$, Shinhung, Seoul, Korea). Experimental implants were coated with ErhBMP-2 (Cowellmedi, Busan, Korea) at a concentration of 1.5 mg/ml. The concentration of ErhBMP-2 was determined based on previous studies finding that it can stimulate local bone formation.[10,11] Each implant was immersed three times in protein solution for 5 seconds and lyophilized, freeze dried at –40℃, and vacuum dried at a maximum of 20℃.[11]

Thirty-six dental implants with six groups were prepared: ErhBMP-2/RBM, ErhBMP-2/MgO, ErhBMP-2/SLA, RBM, MgO, and SLA implants. Randomly three implant selected in the coated group, respectively that the amount of coating was calculated using the Bradford protein assay (Bio-Rad) to react to the absorbance at 595 nm.[21]

The surface morphologies of the uncoated and ErhBMP-2-coated implants were evaluated by scanning electron microscopy (JSM-5800, JEOL, Tokyo, Japan)

## 2. *In Vivo* Study

### 2.1. Animals

The protocol of this study was approved by the Ethical Committee on Animal Research of the Institute of Gangneung-Wonju National University (IACUC 2010-1). Six New Zealand white rabbits weighing 3,450 ± 180 g (mean ± SD) were used in this study. The animals were housed in separated cages and fed a standard diet. Before surgery, general anesthesia was induced by an intramuscular injection of Zoletil® at 0.4 ml/kg (Virbac Laboratories, Carros, France) and Rumpun at 0.1 ml/kg (Bayer, Leverkusen, Germany). Prior to surgery, the operative sites were shaved and carefully washed with iodine solution. Local anesthesia was induced by injecting 1.8 ml of 2% lidocaine with 1:100,000 epinephrine (Huons, Seoul, Korea) at the location of the tibia where the incision was planned. After surgery, all rabbits received 4 ml/kg gentamicin (Kukje Pharmacy, Sungnam, Korea) intramuscularly. The animals were kept in separate cages and allowed full weight bearing after surgery.

### 2.2. Surgical procedures

A skin incision was made along the proximal one-third of the tibia using sterile

surgical techniques. After full-thickness flap reflection, three holes were drilled about 7 mm apart with copious irrigation. The drilling procedures followed the manufacturer's instructions.

In total, 36 implants were surgically placed. Each rabbit received six different implants (three in each tibias in random circulating order into the left and right sides of the tibia to ensure unbiased comparisons). The middle third of each implant was engaged by the upper cortical bone only.

### 2.3. Fluorochrome labeling

The polyfluorochrome sequential labeling process was used to evaluate the postoperative bone formation and remodeling.[22] After implantation, all rabbits received a subcutaneous injection of polyfluorochrome label with an interval of 2 weeks. The polyfluorochrome labels used in the present study were alizarin red (30 mg/kg; Sigma, St. Luice, USA), calcein green (10 mg/kg, Sigma), and tetracycline (60 mg/kg, Sigma).

### 2.4. Preparation of the specimens

The rabbits were euthanized by an excess dose of sodium pentobarbital at 8 weeks after inserting the implants, and specimens comprising the implants plus surrounding tissues were removed *en bloc* from the tibia. The samples were fixed by

immersion in a 10% neutral-buffered formalin solution (Accustain, Sigma-Aldrich, Steinheim, Germany) for 1 day, then dehydrated in a graded series of ethanol solutions, and embedded in methylmethacrylate resin (Technovit 7200 VLC, Kulzer, Friedrichsdorf, Germany). After dehydration, the specimens were polymerized in a light-based polymerization unit (Exakt System, Exakt Appartebau, Norderstedt, Germany). The implants were cut mid-axially in a buccal-lingual plane into 200-µm-thick sections using a band saw with a diamond blade (Exakt-Cutting Grinding System, Exakt Appartebau). The final section was ground to no thicker than approximately 20 µm using an Exakt microgrinder, and polished to an optical finish utilizing the cutting-grinding technique described by Donath and Breuner.[23]

All sections were first examined by immunofluorescence microscopy (Leica Microsystems, Wetzlar, Germany), and then they were stained with 1% toluidine blue solution and examined by optical microscopy (BX-50, Olympus America, Melville, NY, USA).

### 2.5. Analysis of the specimens

One masked examiner using optical microscopy analyzed the histomorphometric measurement. Histomorphometric analyses were performed to obtain additional information on the quality of the implant–tissue interface. The data were quantified as the percentage of the BIC for (1) the bone contact in each/all threads and (2) the bone

contact in the cortical bone. The percentage of the total mineralized bone tissue within the threads [referred to as the bone area (BA)] in the cortical region was also calculated. The new bone area (NBA) within the implant threads in the endosteal region was quantified.

## 3. Statistical analysis

One-way analysis of variance was used to analyze the differences in bone formation between all groups, followed by individual *post hoc* comparisons using Duncan's test. Statistical significance was established at the 95% confidence level. SPSS (version 18.0 for Windows, Chicago, USA) was used for data analysis.

# Ⅲ. Results

## 1. *In Vitro* finding of ErhBMP-2 coated implants

Amount of coated ErhBMP-2 was 9.6±0.4 μg for the MgO implant, 14.5±0.6 μg for the RBM implant, and 29.9±3.8 μg for the SLA implants. Fig.1 shows scanning electron microscopic images of the uncoated and ErhBMP-2 coated implants.

## 2. Clinical findings

The postoperative healing was uneventful in all rabbits, with no cases of implant exposure or loss. No clinical differences were detected between the six groups.

## 3. Histologic findings

After 8 weeks of healing, all implants were histologically in direct contact with the surrounding cortical bone along the upper parts of their threads (Fig. 2). In some specimens, there was overgrowth of cortical bone, and this was greater in the ErhBMP-2/RBM and ErhBMP-2/MgO implants than other implants.

## 4. Histomorphometric analysis

Table 1 lists the results of the histomorphometric measurements. Considering the entire implant, mean bone-implant contact (±SD) for the ErhBMP-2/RBM

(35.4±5.1%) and ErhBMP-2/MgO (33.4±13.2%) implants was significantly greater compared with RBM (23.6±6.2%) and MgO (24.9±2.7%) implants ($p<0.05$). However, ErhBMP-2/SLA implants (19.1±7.2%) showed slightly lower bone-implant contact compared with SLA implants (23.4±3.8%; $p>0.05$). Considering mean bone-implant contact in cortical bone and bone area within the threads, there were no significant differences between ErhBMP-2 coated and uncoated RBM and MgO implants. ErhBMP-2/SLA implants (32.9±7.8%) showed lower bone-implant contact than all other implant variations (range 39.9±18.1% - 51.3±9.2%; $p<0.05$). Similarly there were no remarkable differences in new bone area with minor differences between implants.

## 5. Fluorochrome label analysis

Figure 3 shows polyfluorochrome-labeled bone observed under a fluorescence microscope. The lines of different colors indicate continuing osteogenesis. The polyfluorochrome labels revealed that the patterns of osteogenesis and remodeling differed between the ErhBMP-2-coated and uncoated implants. Bone remodeling occurred in the periosteum area in the uncoated implants (RBM, MgO, and SLA), but was minimal in the regions in contact with the implant surface. However, in the ErhBMP-2/RBM and ErhBMP-2/MgO implants, bone remodeling occurred not only in the periosteum but also in the contacting bone area with the implant threads.

# IV. Discussion

The present study was designed to evaluate the bone response to ErhBMP-2 on three different surface-modified commercial implants. Despite successful clinical trials of rhBMP-2, which have led to its clinical use, the dose, delivery technologies, and conditions that would optimize the stimulation of bone growth are not fully understood.[5,7,16,24] Hypothetically, dental implants coated with rhBMP-2 would stimulate local bone formation and osseointegration in sites of poor bone quality or in need of augmentation. Sykaras et al.[25] observed that bone to implant contact was higher in experimental implants (hollow chamber implant filled with 20 μg of rhBMP-2 with a bovine collagen carrier) than in control implants. Huh et al.[11] described that the ErhBMP-2 coated anodized implant significantly increased implant stability on completely healed alveolar ridges. All of these studies have shown that rhBMP-2 can improve alveolar repair, regeneration, and dental implant healing, which is in agreement with the results obtained in the present study.

Previous studies have mainly evaluated TPO implants coated with CrhBMP-2,[12,14,15,24] whereas the present study used three dental implants with different surfaces (RBM, MgO, and SLA) with/without ErhBMP-2 (1.5 mg/ml). The concentration of ErhBMP-2 was determined based on previous studies finding that it can stimulate local bone formation.[10,11] Wikesjö et al.[10] demonstrated in a mongrel dog model that

sites receiving TPO implants coated with rhBMP-2 at 0.75 or 1.5 mg/ml showed local bone formation including vertical augmentation. However, sites receiving TPO implants coated with rhBMP-2 at 3.0 mg/ml exhibited more immature trabecular bone formation, seroma formation, and peri-implant bone remodeling, resulting in undesirable implant displacement. Huh et al.[11] observed that in a beagle dog model, implants coated with ErhBMP-2 at 0.75 and 1.5 mg/ml exhibited significant vertical bone formation and increased implant stability compared with the control group; the amounts of ErhBMP-2 coated in these groups were 10 and 20 μg, respectively. No adverse effects were reported.

Our experimental hypothesis was that the amount of ErhBMP-2 coating would be varied with the implant surface morphology and surface roughness, and this might affect local bone formation and remodeling. All of the implants in the present study were immersed three times in ErhBMP-2 solution (1.5 mg/ml) for 5 seconds and then lyophilized, which resulted in 9.6±0.4, 14.5±0.6, and 29.9±3.8 μg of ErhBMP-2 being coated on the MgO, RBM, and SLA implants, respectively. The difference in the amounts coated—despite using the same concentration of ErhBMP-2 and the same procedure in each implant—was probably due to the surface morphology and roughness variable of the groups; for example, the surface was more irregular and rougher for the SLA implant than for the RBM and MgO implants (Fig. 1). Rougher surface has enlarged surface area for ErhBMP-2 absorption.

In this study, the mean BIC values for ErhBMP-2-coated implants other than the ErhBMP-2/SLA implant (35.4% for ErhBMP-2/RBM and 33.4% for ErhBMP-2/MgO) were significantly higher than those for uncoated implants (23.6% for RBM, 24.9% for MgO, and 23.4% SLA). The mean BIC value was lower for the ErhBMP-2/SLA implant (19.1%) than for the SLA implant. The BIC value for cortical bone and the BA did not differ significantly between the ErhBMP-2-coated and uncoated RBM and MgO implants; however, the values for the SLA implants were lower in the ErhBMP-2-coated implant than in the uncoated implant. The NBA did not differ significantly between the ErhBMP-2-coated and uncoated implants (Table 1).

Our results suggest that appropriate amount of coating the implant surface with ErhBMP-2 can increase the initial growth of new bone around an endosseous implant and promote bone remodeling around the implant threads, although its effect on cortical bone is minimal. However, overdose of ErhBMP-2 inhibit bone formation like SLA implant. This is same results on previous studies.[10,16] In this study, although same concentration of ErhBMP-2 (1.5mg/ml) was used, experimental results were showed different according to implant surfaces. This difference was probably due to different dental implant surface topography and difference in experimental animals (dog versus rabbit) between studies. However, it is uncertain whether loading amount of ErhBMP-2 is optimal. Further research should be performed using various loading amount depending to experimental animals.

The results obtained in this study using fluorochrome labeling method showed that the pattern of osteogenesis and remodeling differed between the ErhBMP-2-coated and uncoated implants. In the ErhBMP-2-coated implants other than ErhBMP-2/SLA (i.e., ErhBMP-2/RBM and ErhBMP-2/MgO), mineralization occurred not only in the periosteum but also in the surface bone in contact with the implant threads. However, in the uncoated implants (RBM, MgO, and SLA), mineralization occurred mainly in the periosteum area (Fig. 3). The two ErhBMP-2-coated implants (i.e., other than ErhBMP-2/SLA) showed stronger fluorochrome labeling. Remodeling near the periosteum reflects mainly new bone formation, whereas remodeling of the bone surface in contact with the implant thread is thought to promote osseointegration. Therefore, the presence of ErhBMP-2 at appropriate concentrations/doses will help to promote osseointegration.

# V. Conclusions

Within the limits of this study, absorbed ErhBMP-2 dose varies with implant surface characteristics in turn influencing local bone formation/remodeling.

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# Legends

**Figure 1.** Representative scanning electron microscopy images of the uncoated and ErhBMP-2-coated implants (original magnification ×5000). a, ErhBMP-2/RBM; b, ErhBMP-2/MgO; c, ErhBMP-2/SLA; d, /RBM; e, MgO; f, SLA.

**Figure 2.** Histologic images of representative implants after 8 weeks of healing in the tibia (1% toluidine blue staining; original magnification ×100). The BIC of cortical bone appears to be highest in panel b, followed by panels e, d, f, d, a, and c. a, ErhBMP-2/RBM; b, ErhBMP-2/MgO; c, ErhBMP-2/SLA; d, RBM; e, MgO; f, SLA.

**Figure 3.** Fluorochrome-labeled bone at 8 weeks after implant installation (original magnification ×40). a, ErhBMP-2/RBM; b, ErhBMP-2/MgO; c, ErhBMP-2/SLA; d, RBM; e, MgO; f, SLA. Alizarin, calcein, and tetracycline are represented by red, green, and yellow color bands, respectively. Bone remodeling appears to be greatest in panel a, followed by panels b and d. Panel c exhibits inhibition of bone remodeling. The ErhBMP-2-coated

implants (a & b), except for ErhBMP-2/SLA (c), exhibit bone remodeling not only in the periosteum but also in the surface bone in contact with the implant threads. However, uncoated implants exhibit bone remodeling in the periosteum area.

# Tables

**Table 1. Histomorphometric analysis [mean (SD)]**

| Groups | BIC (%) | BIC of cortical bone (%) | BA (%) | NBA (%) |
|---|---|---|---|---|
| ErhBMP-2/RBM | 35.4 (5.1)[a] | 39.9 (18.1)[a] | 71.0 (14.8)[a] | 51.7 (1.6)[a] |
| ErhBMP-2/MgO | 33.4 (13.2)[a,b] | 51.3 (9.2)[a] | 83.3 (5.8)[a] | 50.5 (10.5)[a] |
| ErhBMP-2/SLA | 19.1 (7.2)[c] | 32.9 (7.8)[b] | 52.6 (14.2)[b] | 39.1 (7.1)[b] |
| RBM | 23.6 (6.2)[b,c] | 45.7 (14.3)[a] | 83.1 (5.7)[a] | 47.8 (8.8)[a,b] |
| MgO | 24.9 (2.7)[b,c] | 50.8 (11.6)[a] | 80.5 (12.3)[a] | 49.9 (9.9)[a] |
| SLA | 23.4 (3.8)[b,c] | 45.7 (18.4)[a] | 69.8 (22.7)[a] | 42.2 (2.3)[a,b] |

The same superscript letters indicate the values that are not significantly different ($P$>0.05).

BA, bone area; BIC, bone-to-implant contact; NBA, new bone area.

# Figures

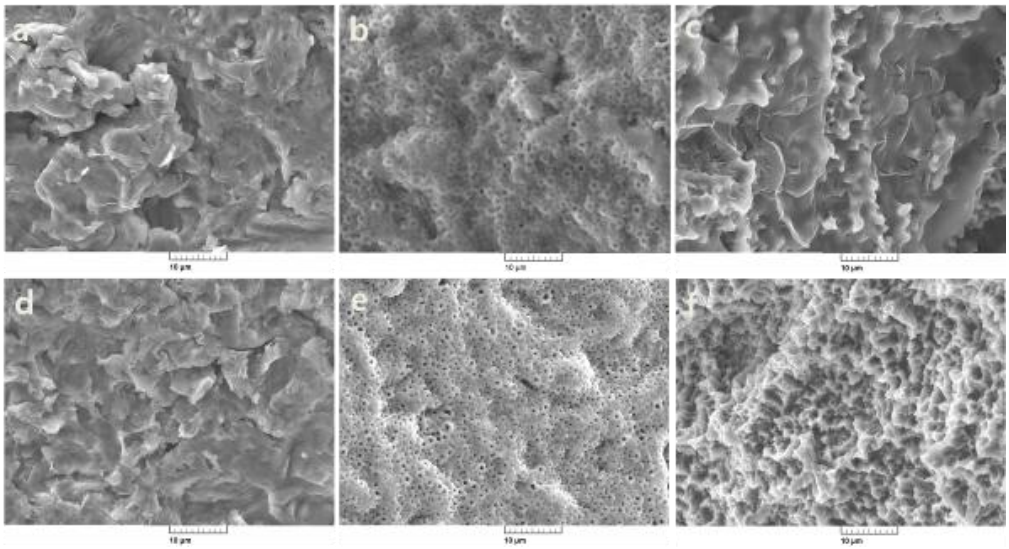


**Figure 1**

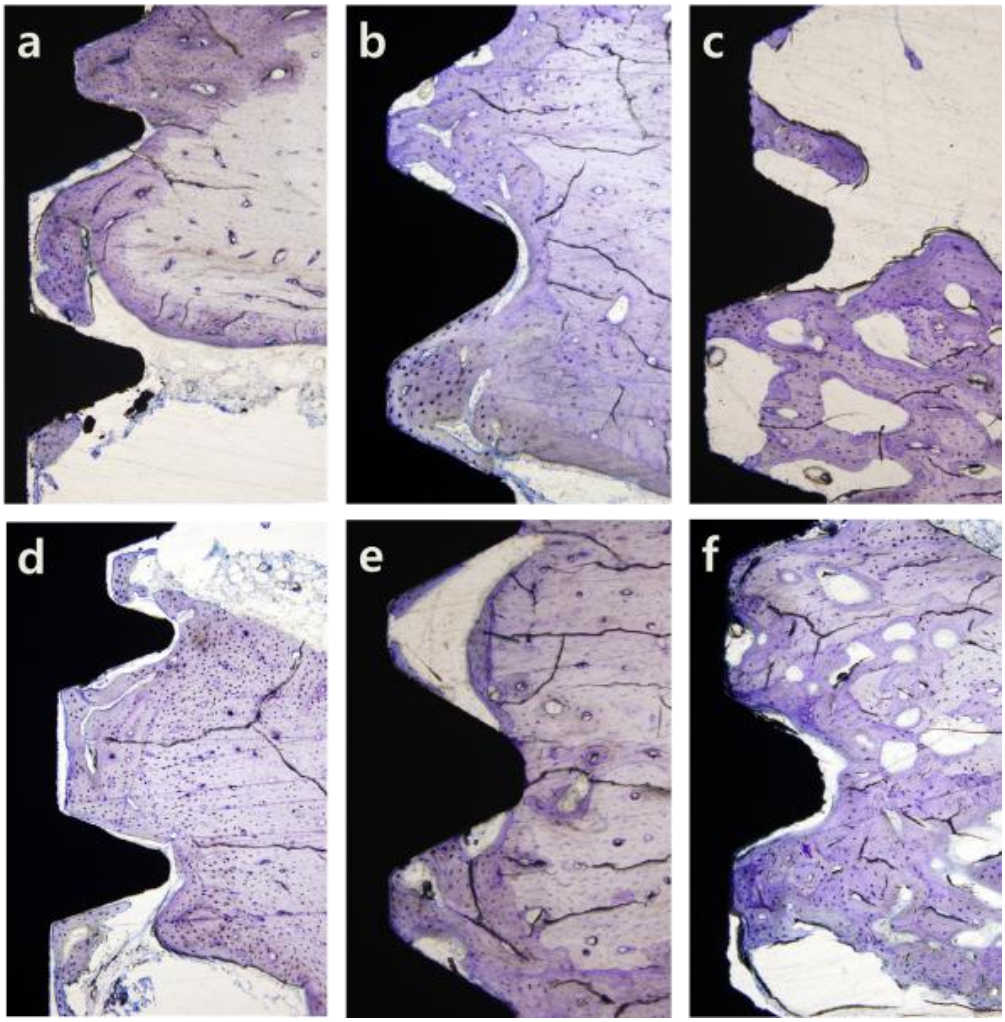


**Figure 2**

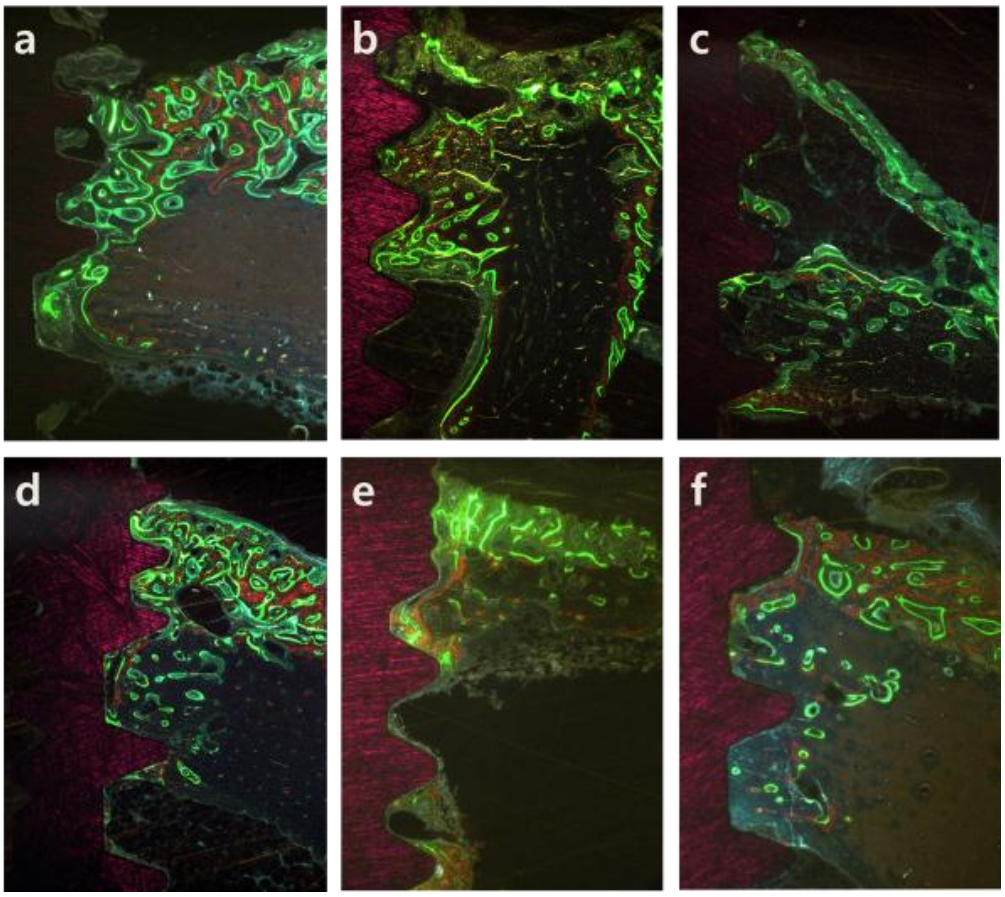


**Figure 3**

국문요약

# 다양한 표면의 치과용 임플란트에서 ErhBMP-2 코팅에 따른 골 반응 변화

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**이 재 관**

최근 치료기간을 단축시키고 골유착 능력을 증진시키기 위해 성장인자와 같은 생물학적 활성 인자들을 임플란트 표면에 적용하려는 연구가 진행되고 있다. 골과 연골의 형성과 재생을 유도하는 조절인자인 골형성유도단백질 (bone morphogenetic proteins; BMPs)은 transforming growth factor-β(TGF-β) superfamily 에 속하는 복합기능의 성장인자로써, BMP-2, -4, -5, -6, -7 등이 골유도성이 있다고 밝혀졌다. 특히 재조합 DNA 기술로 얻어지는 인간재조합 골유도형성단백질 (recombinant human BMP; rhBMP)-2, -7 의 골유도 능력이 가장 우수하다고 보고되어, 이를 이용한 많은 연구가 진행되고 있다.

대부분의 rhBMP-2 는 Chinese hamster ovary (CHO) cell 을 이용하여 생산되고 있는데, CHO cell 을 이용한 rhBMP-2 의 재조합 기술은 비용적 비효율성 때문에 임상에서 널리 사용되는데 한계를 가진다. 이에 최근에는 이러한 문제들을

해결하기 위해 *Escherichia coli* (*E. coli*)를 이용한 rhBMP-2 (ErhBMP-2) 재조합 기술이 개발되었다.

이번 연구에서는 다양한 표면의 치과용 임플란트에 기존의 연구에서 가장 적절하다고 평가된 농도의 ErhBMP-2 코팅을 통해 표면처리 방법에 따른 ErhBMP-2 의 적용 가능성을 평가하였다.

표면처리 방식이 다른 3종류의 치과용 임플란트 (resorbable blasting media; RBM, sandblasted large grit and acid-etched; SLA, Mg-incorporated oxidized; MgO)에 1.5 mg/ml의 농도를 갖는 *Escherichia coli*-derived rhBMP-2 (ErhBMP-2)로 코팅 처리를 하였다. 준비된 6군의 임플란트 (ErhBMP-2/RBM, ErhBMP-2/MgO, ErhBMP-2/SLA, RBM, MgO, SLA)를 6마리의 가토 경골에 좌측 또는 우측에 각각 대조군과 실험군으로 3개씩 식립하였다. 식립 후 골의 재형성 과정을 확인하기 위해 2주에 alizarin, 4주에 calcein, 6주에 tetracycline을 주입한 후 8주에 희생시켜 조직계측학적 검사를 시행하였다.

각각의 임플란트에 적용된 ErhBMP-2의 양은 9.6±0.4 μg/MgO, 14.5±0.6 μg/RBM, and 29.9±3.8 μg/SLA이었다.

ErhBMP-2/RBM (35.4±5.1%) 와 ErhBMP-2/MgO (33.4±13.2%) 임플란트는 RBM (23.6±6.2%), MgO (24.9±2.7%)에 비해 더 높은 골-임플란트 접촉 (bone-implant contact)을 보였다. 그러나 ErhBMP-2/SLA (19.1±7.2%) 임플란트는 SLA (23.4±3.8%; $p > .05$)임플란트에 비해 더 낮은 골-임플란트 접촉을 보였다. 면역형광검사 결과, ErhBMP-2/RBM 와 ErhBMP-2/MgO 임플란트는 골막뿐만 아니라 나사선

주위에서도 활발한 골형성과 골재형성이 관찰되었다. 반면, ErhBMP-2/SLA 임플란트 주위에서는 골형성 과정이 억제됨이 관찰되었다.

이 실험을 통하여, *E.coli*에서 생산된 rhBMP-2는 임플란트의 표면 특성에 따라 흡수되는 양이 달라질 수 있으며, 이로 인해 골형성과 재형성 과정에 유의한 차이를 가져올 수 있음을 알 수 있었다.

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**핵심되는 말** : 골형성유도단백질; 치과용 임플란트; 면역형광 검사