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Runnning heads: Periosteal expansion osteogenesis using SMA device

Alveolar bone augmentation is one of the standard treatments for dental implantation when alveolar bone volume is insufficient. A relevant vertical and/or horizontal defect of the alveolar ridge is still a challenge for appropriate implant placement and predictable long-term results.

Autogenous bone grafting is considered the gold standard for maxillofacial bone reconstruction[1,2]. However, this technique may be associated with donor site morbidity and resorption of the grafted bone, and it cannot be used for simultaneous soft tissue augmentation. Thus, the amount of bone augmentation is usually limited.

In contrast, distraction Osteogenesis (DO) is an alternative method that uses a biological process in which new bone formation occurs between segments that are gradually separated[3,4]. This gradual traction of pedicled bone fragments is followed by simultaneous osteogenesis (bone) and histogenesis (functional soft tissue matrix). However, disagreement exists regarding the various treatment parameters, such as surgical technique, type of distraction device, and minimal bone height and width necessary to perform distraction.

Recently, osteogenesis by periosteal distraction or elevation without corticotomy for bone augmentation has been suggested[5-9]. This method is based on the concept that tensile strain on the periosteum, which causes tenting of the subperiosteal capsule, is sufficient to produce bone formation, without corticotomy or local harvesting of the bone. These studies indicated a new technical aspect of DO or tissue expansion, with the controlled guided formation of new bone.

Previously, we investigated the utility of periosteal expansion osteogenesis (PEO), the same concept as periosteal DO or elevation, using a highly purified β-tricalcium phosphate (β-TCP) block, instead of titanium devices, in a dog model. We found that newly formed bone at the gap between the original bone and β-TCP block, and the β-TCP block, acted as a space-maker under the periosteum. This suggests the possibility to inducing newly formed bone with no autogenous grafting or osteotomy. However, it needs mechanical activation, as does a DO protocol with a turning device penetrating the mucosa or skin. Such penetration of soft tissue around the augmented area can cause wound dehiscense or exposure of the device, and subsequent infection. Considering the ideal conditions for acquiring sufficient bone, a complete capsule under the periosteum is required.

Many studies have done to make novel distraction device that expand automatically

and automatically, for example motor-driven, spring-mediated and hydraulic devices[10]. However most of those devices were too big to implantation. Clinical useful device that has an automated activity require specific parameters; small size, easily implantable, fully buried, biocompataible, sufficient force generation and maintenace. NiTi implants have been used for cardiovascular and orthodontic treatments[11,12]. However these materials are not used for bone augmentation, although a few animal studies have shown the possibility of using them for jaw elongation or alveolar bone augmentation with a DO technique. And those were used as spring device, so it is difficult to control the activation rhythm and distraction or expansion vector. To create the ideal space with no manual activation, we developed a simple self-activated mesh device made of Ni-Ti shape-memory alloy (SMA) for periosteal expansion. The present study evaluated the use of this self-activated using SMA device with a forcus on its effects in the region under the periosteum.

MATERIALS AND METHODS

Japanese white rabbits (all male, 3 - 3.5kg) were used and were divided into four groups of three according to the time of sacrifice and with or without activation. The protocol and guidelines for this study were approved by the Institutional Animal Care and Use Review Committee of Kyushu Dental College, Kitakyushu, Japan.
In the control group, the device was only inserted with no activation, and others in the experimental groups, it was inserted and activated after a latency period. Groups were also defined for consolidation periods of 5 and 8 weeks after surgery.

Device description

The device consisted of Ni-Ti materials (Ni; 56.1, Ti; balance, Fe;≦ 0.05, O;≦ 0.05, C;≦ 0.03, N;≦ 0.02, wt.%). The form of the mesh device was 5mm width, 25mm length and 0.275 mm thickness. The pre-curved form was designed that the middle point was 4mm above from the baseline [Figure 1].
The deformation behavior of the SMA mesh plate was measured by a compressive test [Figure 2]. The plate was fixed on an Instron-type testing machine (Model AG-I; Shimadzu Co., Japan), and compressive stress was applied perpendicularly to the plate at a cross-head speed of 1.0 $mm \cdot min^{-1}$. Compressive load (σ) and displacement (l) was

calculated when the plate became completely flat.

Average compressive load and displacement was summarized in Table 1. Width of the center and the whole of the plate are 5 and 15 mm, respectively. If it is assumed that the former has the same size as the latter, compressive load required for the same displacement as the latter is calculated as 2.7 N (= 0.9÷5 x 15). This is lower than the measured compressive load of whole the plate. This is attributed to the face that the center of the plate has porous structure.

Surgical protocol

The animals were anesthetized by intramuscular administration of ketamine hydrochloride (60 mg/kg Ketalar, Sankyo, Tokyo), followed by diazepam (5 mg) and atropine sulfate (0.5 mg), without endotracheal intubation. Before the operation, 10 mg/kg pentobarbital sodium was injected intravenously. In addition, 1.8 ml of local anesthetic (2% xylocaine and epinephrine 1:80000, Dentsply Sankin, Tokyo, Japan) was used during all surgical procedures. Immediately after the operation, the animals received cefazolin sodium (20 mg/kg) subcutaneously, which was continued until postoperative day 3.

The operation was performed under standard sterile conditions. The forehead of the animal was shaved and disinfected with 1% iodine sodium. After a U-shaped skin and V-shaped periosteal incisions were made in the forehead region, the frontal bone of the animal was exposed following the careful elevation of the periosteum. The device was inserted under the periosteum [Figure 3(A)]. In the experimental group, the device was pushed, bent, and attached to the bone surface and fixed with a titanium screw (diameter: 2.0mm, length 4mm) [Figure 3(B)]. In control group animals, the device was only inserted under the periosteum. After irrigation with saline, the periosteum was positioned back in its original place and stabilized by suturing with 5-0 Vicryl. The skin was made using 4-0 Vicryl [Figure 3 (C)].

Postoperative protocol

All rabbits were given water and normal rabbit food postoperatively. After 14 days a soft tissue incision of 2 mm long was made over the screw and a driver was inserted for its removal of it in the experimental group [Figure 3(D)]. The wound was closed using

5-0 Vicryl after screw removal in the experimental group. Rabbits were sacrificed after a 3- and 6- week consolidation period with a lethal dose of thiopental sodium. In control group, the timing of the sacrifice was the same as in the experimental group, so it was done at 5 and 8 weeks after the operation. The cranial bone was removed and fixed for 14 days in 10% buffered formalin.

Tissue preparation and histological evaluation

Cranial bone tissue was evaluated by soft focused X-ray CT (Comscantechno, Co, Ltd, Yokohama, Japan) under electrical conditions of 65 μA and 70 kV. Measurements were made on three vertical images per specimen, closest to the centre of the device. In each image, the area occupied by the new bone was measured using image analysis software (Image J, ver.1.44; NIH, Bethesda, MD). The complete area underneath the SMA device was defined as "the expanded volume" (EV). The area of mineralized tissue in the EV was defined as "the total bone volume" (TBV). The percentage ratio of EV/TBV was calculated to assess the extent of new bone growth.

Specimens were fixed without decalcification and then immersed in Villanueva bone stain solution (Maruto, Tokyo, Japan). Then the specimens were then dehydrated through a graded ethanol series, embedded in methylmethacrylate (Wako Pure Chemical Industries, Osaka, Japan), and cut in 5-μm sections (Exact, Mesmer, Ost Einbeck, Germany).

Statistical analysis

Statistical analyses were performed using the SPSS software (ver. 10.0 ; SPSS Inc, Chicago, II, USA). Normality and homogeneity were analysed with variance tests. A paired *t* test was used to analyse the area of newly formed bone and the ratio of EV/TBV of all groups. The level of significance was chosen in all statistical tests was set at $P < 0.01$.

RESULTS

No complications related to the materials used at the sites of intervention, before, during, or at the end of the experimental phase or infection within or around the device were observed in any animal. Upon screw removal, the device was activated to the

original position immediately in two animals. They were concealed under the soft tissue during activation and the consolidation period until the time of sacrifice and no clinically active inflammation was observed around the SMA device.

Five and eight weeks after operation, soft focused X-ray CT images showed that the newly formed bone was less radiopaque than the original bone. Newly formed bone tissue was hardly observed in the control group at postoperative 5 weeks. The peak of newly formed bone was located under the centre of the device [Figure 4(A)]. The dome shape bone outlined from original bone in the experimental group [Figure 4 (B) (D)]. The quantitative data by the area and the occupation of newly formed bone (TBV/EV) indicated that the experimental group had a higher volume of new bone than the control group at each consolidation period ($P < 0.01$) [Table 2]. With increasing bone consolidation period, the date was also relatively increased but there were no static difference between both of time course.

Five weeks after operation, some newly formed bone was observed and most of the subperiosteal space underneath the device was filled with fibrous tissue with no inflammatory cell reaction, and a thin layer of immature bone was observed at the outer surface of original skull bone in the control group [Figure 5(A)]. In the experimental group, a thin osteogenic layer, same as in the control group, was also observed along with an obvious, prominent, newly formed bone trabeculae connecting the layer to the original bone. [Figure 5(B)].

Eight weeks post-operation, similar histological patterns were observed in the control group [Figure 5(C)]. A layer of immature bone and a bridge-like structure were observed. However, quantitative evaluations showed no difference between them in the time course. In the experimental group, multiple dome-shape bones, outlined by thin and scattered bone trabeculae were clearly observed under the SMA mesh device [Figure 5(D)]. These newly formed bone trabeculae were observed in the centre of the SMA device, and the domed shape of the newly formed bone trabeculae was similar to the curved shape of the SMA device in some specimens.

Discussion

DO is successful because, under appropriate levels of stimulation, periosteal

mesenchymal stem cells differentiate into osteoblasts and produce an early subperiosteal callus within the osteomized gap [13,14]. The most recent concept of periosteal DO is also based on the potential of the periosteum to differentiate into osteoblasts to fill the space over the underlying bone.

Previous reports of periosteal DO showed new bone formation in the gap created by the devices. However the disadvantages for clinical application still exist. One is that most devices penetrate the skin or mucosa and need manual mechanical activation to create the space between the periosteum and underlying bone. It is also difficult to close the wound with the periosteum over a bulky device. Sufficient closure with the periosteum is an important factor to acquire newly formed bone as a result of periosteal DO. The device used in this study consisted of a thin NiTi mesh device (0.25mm thick) and had the advantage of acquiring an ideal capsule under the periosteum. This thin SMA device can be used as an automated and fully internalized distraction device, which might resolve many complications with minimal invasion.

The histological findings demonstrated that newly formed bone originated mainly from the underlying original bone. Even in the control group, a thin layer of immature bone was observed at the surface of the bone. It seemed that progenitor cells were from the blood and osteoblasts were provided from the original bone. In addition, the prominent newly formed bone under the device was observed in the experimental group. The location of the main prominence was at the same level as the mid point of the device. It seemed that the pressure from the overlying soft tissue affected the ossification from the original bone and the excess tension under the periosteum prevented the production of newly formed bone. However, Zakaria et al reported that the relatively thick trabecular bone was observed in the segment near to fixed end[9]. In this study, newly formed bone was observed more in the middle part than at the end. A fixation screw was placed in the centre of the device and removed after a latency period of 2 weeks, so the end of the device was not fixed in this study. In the experimental group, at postoperative 8 weeks, the dome shape of the newly formed bone trabeculae was similar to the curved shape of the SMA device in some specimens. It seems that bone regeneration was induced by the gradual expanding force of the elasticity of the SMA device. Lethaus et al. showed that the newly formed bone in the static periosteal shielding procedure was almost the same as that in the dynamic periosteal elevating procedure[15]. This is different than the present results. They used pig forehead and its skin and soft tissue was much thicker than the

rabbit tissue we used. Also, they put every type of devices were put on the same forehead, the tension against the each device may have been less than with the single device used in this study.

The speed of self-activation after removal of the fixation screw seems to be an important factor in acquiring newly formed bone in this method. Sensimen et al clearly demonstrated that the quality of newly formed bone depended on the distraction speed[7]. Zakaria et al. also reported that the speed of the regenerative space expansion by periosteum elevation should be optimized, and that the speed range of periosteal distraction for bone augmentation was 330 μm per day or less[9]. Measuring the activation speed in this study was difficult, as speed was affected by the form of the device, including the thickness, initial healing around the device, the amount of soft tissue, and body temperature. In addition, only one kind of device was used in this study, so further evaluation is necessary to identify the appropriate form and elasticity of the SMA device.

The role of the mesh-perforations is still a matter of debate. In the previous reports, most of the devices for the periosteal DO or dynamic elevation technique had mesh perforations in the part involved in the traction of the periosteum without standardization of their number or size[5,7,9]. Gosain et al. demonstrated the influence of the periosteal layer on calvarian defects in rabbits[16]. He created a barrier with non-perforated polytetrafluoroethylene membranes that reduced new bone formation in the centre of calvarian defects, but simultaneously enhanced bone growth at the peripheral cranial border. Weng et al. demonstrated increased bone growth using the same membranes to shield the elevated spaces from the periosteum in guided bone regeneration[17]. In the dynamic separating procedure, such as this technique or pariosteal distraction, it seems to be important to have sufficient communication between the periosteum and the underside of the device with appropriate mechanical strength against the overlying soft tissue to encourage new bone formation.

Another issue is that nickel may have toxic effects *in vitro* and *in vivo* at high concentrations. The high nickel content of Ni-Ti might cause biocompatibility problems, due to dissolution of nickel ions or wear particles from the alloy[18]. Thus, long-term application of the Ni-Ti alloy should be avoided, and development of a new device with different materials but with the same properties is expected. Few reports have demonstrated ossification between the bone surface and periosteal tissue created by the SMA device after a latency period based on a distraction concept. Macroscopic and

microscopic observations conducted in this study revealed no pathological change around the SMA device. Nonetheless this nickel toxicity problem has to be addressed before human use. Recently, new Ni-free, Ti- based alloy was examined for application in orthodontic treatment and craniofacial plastic surgery[19,20]. This material may be suitable for human use.

In medical applications, the mechanical properties and degree of elasticity differ in each treatment. In this study, only one device was used with one protocol. The results might have been different if we had used other devices with different elasticity or set a longer/shorter latency or consolidation period. SMA materials have been used for bone regeneration or lengthening of the jaw bone[10,21,22]. However, the material was used in the form of a wire, and there is no previous report of using a mesh or board SMA device for a periosteal DO technique.

To the best of our knowledge, this is the first report of newly formed bone in the gap created by the self-activated force using a SMA mesh device. Further studies are needed to provide more information about the newly formed bone and for subsequent use in clinical situations. Improvement in device design and mechanical properties will enable three-dimensional control in craniomaxillofacial surgery and orthopaedic surgery. The use of self-activated devices for the periosteal expansion technique may make it possible to avoid the donor site morbidity associated with autogenous tissue grafts, trans-skin, or trans-mucosal activation rods, any bone-cutting procedure, and the following intermittent activation procedure of normal DO.

Figure legends

Fig. 1: Image of SMA device

Fig. 2: Scheme of the compressive test. σ: Compressive load *l*: Displacement

Fig. 3: Image of surgical procedure. SMA device under periosteum (A). fixation with titanium screw at the bended position (B). closure with periosteum over the device (C). , image at the screw removal after latency period for 2 weeks (D).

Fig. 4 : Soft focused X-ray CT images showing cross sectional view of few bone over the original bone at postoperative 5 weeks in control group (A). Dome shape bone outlined from original bone was observed at postoperative 5 and 8 weeks in the experimental group (B)(D). A thin newly formed bone was observed on the original

bone at postoperative 8 weeks in control group (D).

Fig. 5: Representative histological images stained with Villanueva bone stain for control and experimental group Scale = 300 μ in A,B,C,D, 30 μ in E,F. A thin newly formed bone layer was seen over the original bone at postoperative 5 weeks in control group (A). A prominent newly formed bone connected with thin layer same as (A) was observed at postoperative 5 weeks in the experimental group (B). A layer of newly formed bone and some bridge-like structure was observed at postoperative 8 weeks in control group (C). A multiple dome shape bone was observed at postoperative 8 weeks in the experimental group (D).

Table 1: Average compressive load and strain of whole the plate and center of the plate

(n=3)

Table 2: Table showing the quantitative data by the area and the occupation of newly formed bone (TBV/EV). * $P < 0.01$

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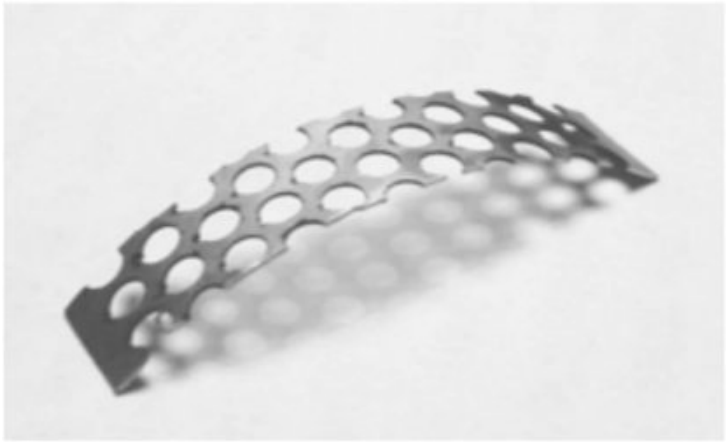

Fig 1

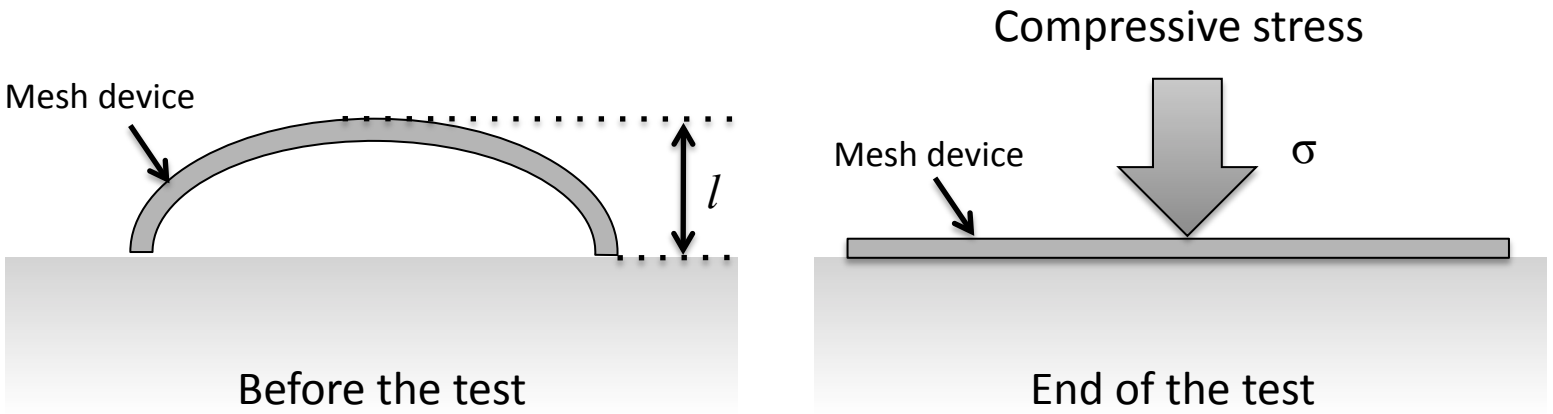
Compressive stress
Mesh device
l
Before the test
Mesh device
σ
End of the test

Fig 2

Figure 3

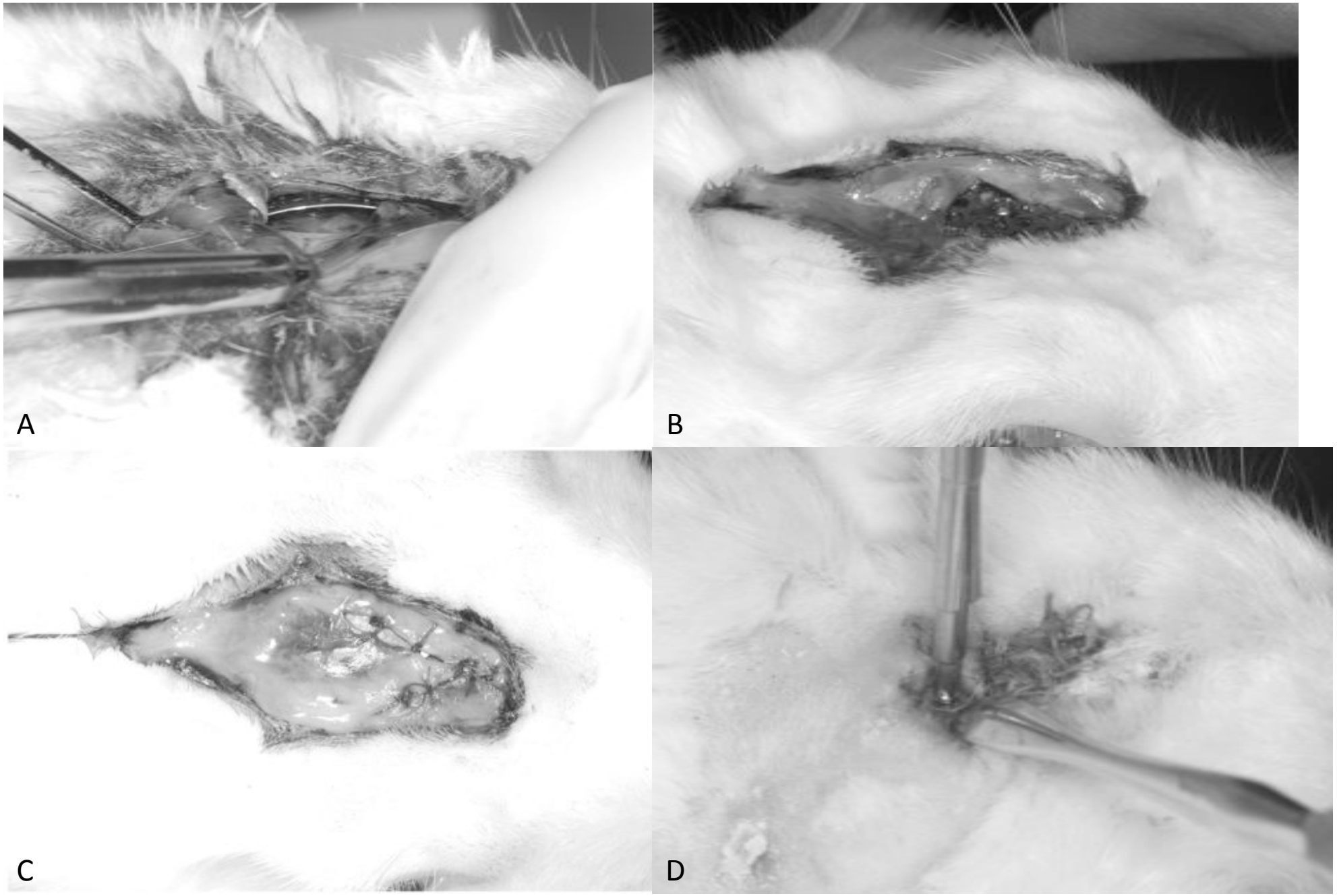

Figure 4

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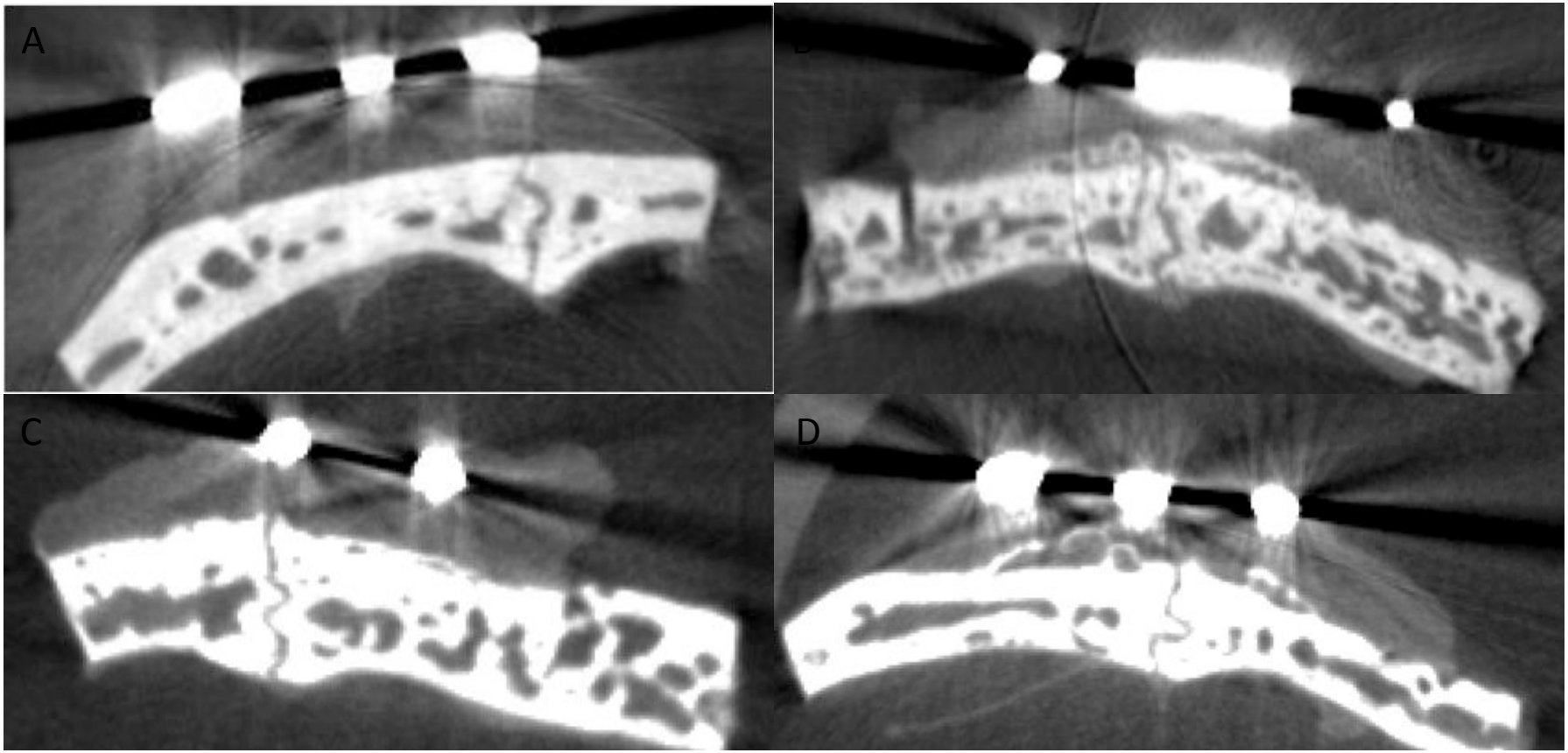

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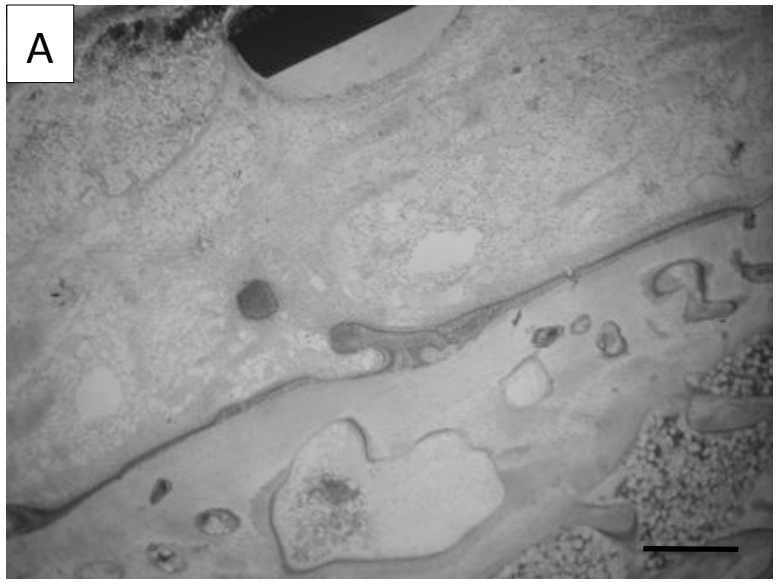
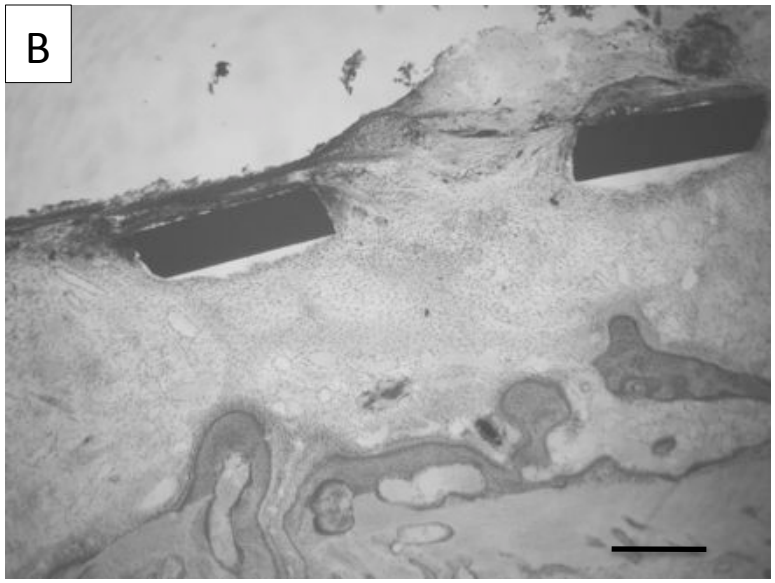
Figure 5





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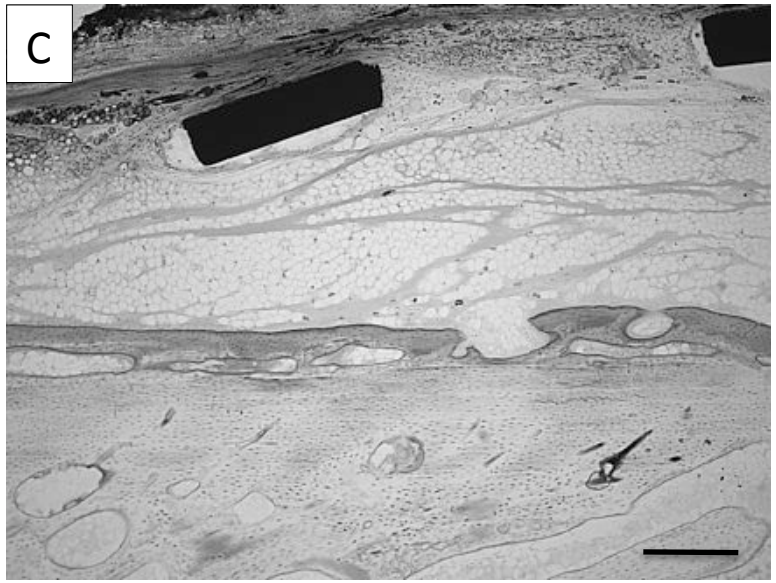

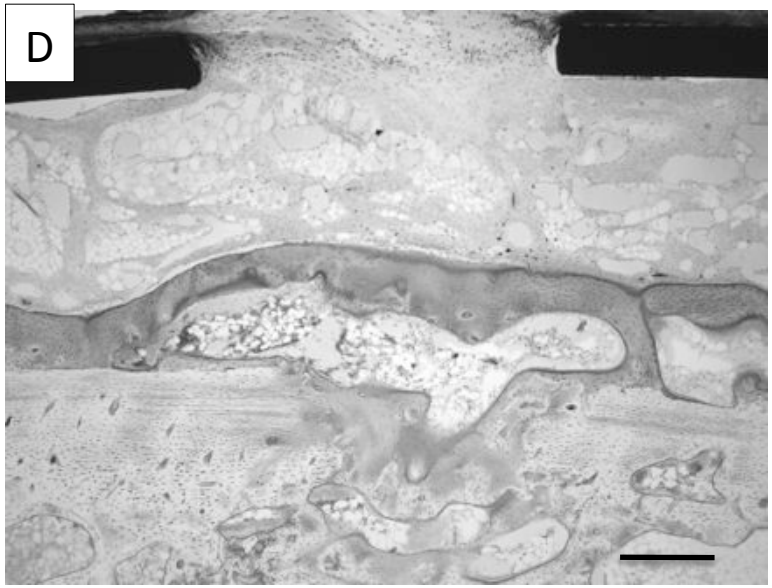

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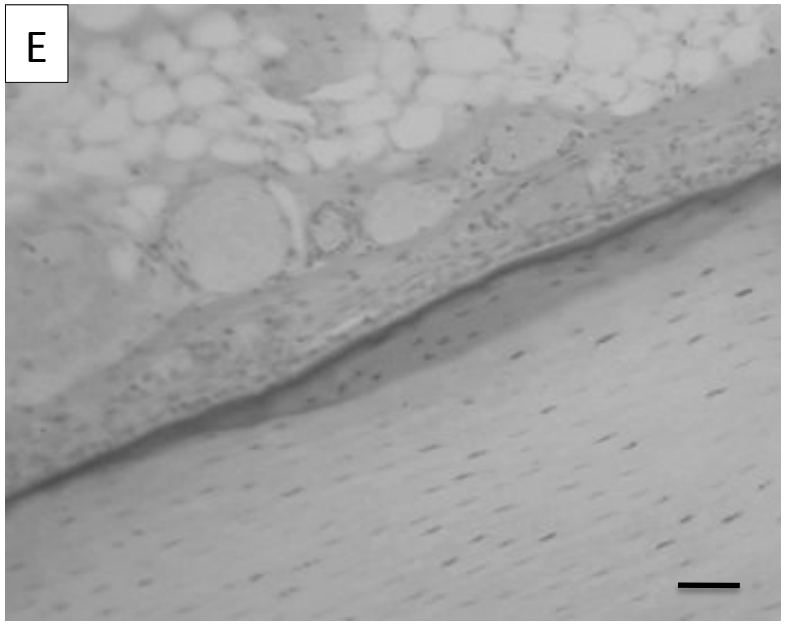
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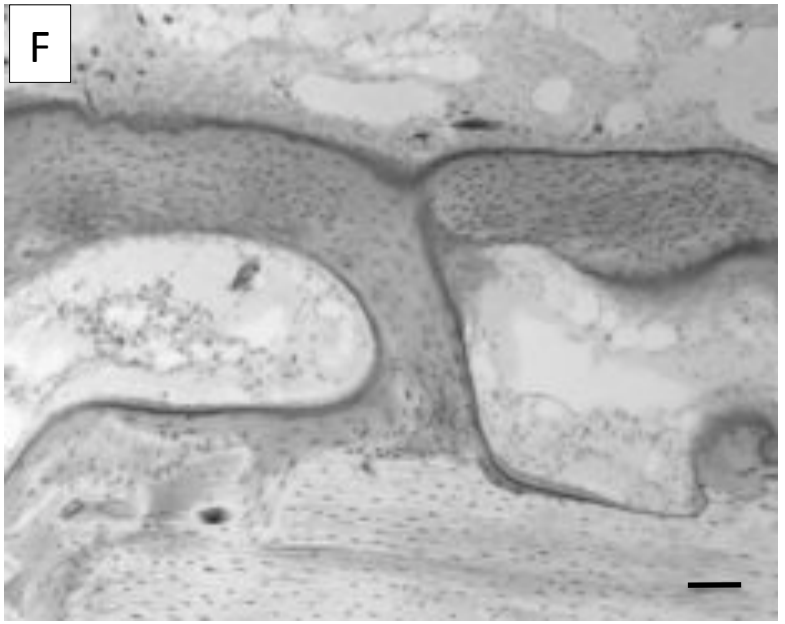
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	Compressive load (σ) / N	Displacement (l) / mm
Whole the plate	4.2	3.99
Center of the plate	0.9	4.05

Table 1

	Postope 5 weeks (mean ± SD)		Postope 8 weeks (mean ± SD)	
	Control	experiment	Control	experiment
Bone area (mm^2)	0.10 ± 0.12	2.14 ± 0.85 *	0.34 ± 0.18	2.90 ± 1.13 *
Ratio of TBV/EV (%)	1.6 ± 1.1	27.3 ± 10.8 *	11.2 ± 4.5	31.1 ± 12.1 *

Table 2