Effects of ultraviolet and alendronate treatment on the osseointegration and mucosal attachment of dental implants

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Effects of ultraviolet and alendronate treatment on the osseointegration and mucosal attachment of dental implants

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2022년 12월

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ABSTRACT

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The purpose of this study is to evaluate the effects of ultraviolet (UV) treatment and alendronate immersion on the osseointegration of dental implants and mucosal attachment of dental implant abutments using a mongrel dog model. Forty-eight sandblasted, large-grit, acid-etched (SLA) titanium dental implants and 48 machined surface healing abutments, and four male mongrel dogs were prepared. Implants and healing abutments

were divided into four groups (n=12 per group). The control group did not undergo additional surface treatments. The UV group was treated with UV for 15 minutes, and the AN group was soaked in 10^{-3} M alendronate for 24 hours. The ANUV group was treated with alendronate, followed by UV irradiation. All implants were placed on the mandible of mongrel dogs, and the animals were sacrificed at 4 and 8 weeks post-operatively. The bone-to-implant contact (BIC), bone density (BD), and connective tissue attachment (CTA) were measured. UV treatment of the SLA implants significantly increased the BIC of the cortical bone. However, the alendronate immersion did not significantly increase BIC or bone density, and there was no synergic effect with the UV treatment. Furthermore, UV treatment and alendronate immersion of machined healing abutments did not significantly increase the CTA. These results revealed that UV treatment on SLA implants can promote the osseointegration of implants, but alendronate immersion is not effective, and mucosal attachment to abutments is not enhanced by UV treatment and alendronate immersion.

Keywords: alendronate, connective tissue attachment, dental implant, dental implant abutment, osseointegration, ultraviolet

Effects of ultraviolet and/or alendronate treatment on the osseointegration and mucosal attachment of dental implants

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I. INTRODUCTION

Dental implants are one of the most useful treatment options for fully and partially edentulous patients. Initial osseointegration of dental implants is essential for treatment success. The rate and quality of the initial osseointegration are intimately related to the surface characteristics of the implants. In particular, the composition, hydrophilicity, and roughness of the implant surfaces are important factors in the implant-tissue interaction and osseointegration.[1] Therefore, various surface treatment methods have been introduced and developed over the past few years to improve the osseointegration of dental implants.

Currently, the SLA(sandblasted, large-grit, acid-etched) treatment is one of the most widely used surface treatment methods for dental implants. Sandblasting, acid-etching, or a combination of both, has been utilized to enhance the microroughness of dental implants. SLA surfaces have been demonstrated to promote bone apposition histologically,[2] and SLA-treated implants have a high removal torque value according to biomechanical testing.[3] Previously, a retrospective analysis revealed a high 10-year survival and success rate.[4]

When titanium is exposed to air, hydrophilicity gradually diminishes by hydrocarbons due to its own characteristics.[5] Previous studies have reported that the degree of osseointegration of implants with hydrophobic surfaces was lower than that of hydrophilic surfaces.[6] Therefore, various methods to increase hydrophilicity by increasing the surface energy of implants have been studied to improve the osseointegration of implants. These include activation using plasma of argon,[7] alkali treatment,[8] and ultraviolet (UV) irradiation.[9-11]

As mentioned, UV irradiation is one way to increase the hydrophilicity of titanium implants. According to a study that applied a push-in test to evaluate the strength of osseointegration, UV treatment of acid-etched miniature titanium implants markedly enhanced osseointegration at 2 weeks after implant placement in a rat model.[9] Another study assessed UV treatment-dependent effects on anodized titanium implants in a rabbit model and reported that the bone-to-implant contact (BIC) and the amount of bone in the thread area were significantly higher in the UV-treated group at 4 weeks after implantation,

but were not significantly different between the groups at 12 weeks after implantation.[10] An *in vivo* experiment that assessed the UV treatment-dependent effects on implant osseointegration using a minipig model also reported that there were no statistically significant differences in the implant stability quotient (ISQ) values at 12 weeks after implantation or the BIC measurement at 24 weeks after implantation.[11] Taken together, these findings indicate that UV treatment may not affect the degree of final implant osseointegration but may have a beneficial effect on osseointegration in the initial phase of implantation.

Furthermore, attempts have been made to use bioactive factors, such as bone morphogenetic proteins,[12,13] fibroblast growth factor-fibronectin fusion protein,[14] and Arg-Gly-Asp (RGD)-peptide-modified polymers[15] for implant surface treatments. There have also been attempts to use bisphosphonates for this purpose. Bisphosphonates are bioactive agents that inhibit bone resorption and ectopic calcification, and are commonly used for the treatment of osteoporosis, Paget's disease, and primary hyperparathyroidism.[16] An earlier study that assessed the use of alendronate in dentistry reported that local application of alendronate on peri-implant defects increased the early bone formation rate in a mongrel dog model.[17] A later study on beagle dogs reported that the BIC percentage was significantly higher in the bisphosphonate-treated titanium implant group than in the non-bisphosphonate-treated group at 12 weeks after implantation.[18] In addition, a rat study compared four different surface treatments on hydroxyapatite-coated titanium implants and reported that, at 3 months after implantation, the bone-implant interface was significantly

higher in all three groups treated with bisphosphonate compared with that in the non-bisphosphate treated group. Of the three bisphosphonate-treated groups, the highest value was found in the zoledronic acid group, followed by the ibandronate group, and the pamidronate group.[19] This series of animal studies indicated that alendronate treatment of implant surfaces may effectively enhance osseointegration.

The soft tissue barrier, which functions as a protective seal between the oral environment and the underlying peri-implant bone, is another important component for successful implant treatment. This soft tissue barrier is composed of two layers, namely, the epithelial attachment and underlying connective tissue attachment (CTA) layers.[20-24] These attachments are known to be important for the maintenance of osseointegration of implants.[22] Thus, studies on mucosal attachment to the abutment have also been reported. A study that examined the mucosal attachment of different abutment materials reported that titanium and ceramic abutments formed epithelial and connective tissue attachments that were 2 mm and 1-1.5 mm high, respectively, whereas gold abutment did not form proper attachments and led to bone resorption.[20] Another study reported that the soft tissues remained stable for 2–5 months with titanium and zirconium abutments, whereas with gold/platinum-alloy abutments, the barrier epithelium shifted apically and marginal bone resorption occurred,[21] indicating that mucosal attachment can vary depending on the surface properties of the abutment materials.

Various surface treatment methods have been studied to improve mucosal attachment. An *in vitro* experiment showed that fibronectin coating of smooth (machined), plasma-

sprayed, and hydroxyapatite-coated titanium surfaces enhanced gingival fibroblast attachment by 2-3 folds and that laminin coating also enhanced gingival epithelial cell binding.[25] Another study reported that cleaning by plasma of argon may enhance cell adhesion to titanium abutments, even at the early stage of soft tissue healing.[26] There was also s study that demonstrated an increased human gingival fibroblast differentiation and adhesion by UV treatment of titanium surfaces.[27] However, it was difficult to find *in vivo* studies that investigated the effects of different abutment surface treatments for enhancing mucosal attachment.

This study aimed to examine the effects of UV-alendronate combined treatment of SLA surface-treated implants on the osseointegration of implants and mucosal attachment of implant abutments from two different perspectives using a mongrel dog model. The null hypothesis is that, at both 4 weeks and 8 weeks after implant placement, there would be no difference in osseointegration or mucosal attachment between the control and UV-treated and/or alendronate-immersed groups.

II. MATERIALS AND METHODS

1. Experimental animals, housing, and husbandry

Four male mongrel dogs (aged 24 months, weighing approximately 30 kg) were used in the present study. Experimental animals were housed at room temperature (20 °C) with humidity of around 50%.

On the day of surgery, medetomidine (0.1 mg/kg, Tomidin, Provet Veterinary Products, Istanbul, Turkey) was injected intramuscularly to sedate each dog. Subsequently, alfaxalone (2.2 mg/kg, Alfaxan; Careside, Seongnam, Korea) was intravenously injected for general anesthesia. Inhalation anesthesia was maintained with 2–2.5% isoflurane, and an electrocardiogram was used for monitoring. For local anesthesia at the surgical site, 2% lidocaine with 1:80,000 epinephrine (2% lidocaine hydrochloride injection; Huons Co., Ltd, Seongnam, Korea) was injected.

Antibiotic administration was performed according to the protocol as follows. On the day of surgery, antibiotics (30 mg/kg intramuscular cefazolin sodium, Yuhan, Seoul, Korea) and anti-inflammatory and analgesic medications (0.5 mg/kg IV; Ketorolac, Hana Pharm., Gyeonggi-do, Korea) were administered for one day. Then, for the following week, antibiotics (13.75 mg/kg; amoxicillin-clavulanate, Boryung Pharmaceutical, Gyeonggi-do, Korea) and an anti-inflammatory and analgesic medication (0.1 mg/kg; meloxicam, Boehringer Ingelheim, Bogota D.C., Colombia) were orally administered. Sutures were removed 1 week after surgery. Following tooth extraction, the dogs were maintained on a

soft diet until they were sacrificed.

2. Ethical considerations

All experimental procedures were reviewed and approved by the Institutional Animal Care and Use Committee (Yonsei Medical Center, Seoul, Korea; Approval No. 2018-0034). The housing protocol suggested by the Association for Assessment and Accreditation of Laboratory Animal Care International guidelines was followed.

3. Experimental procedures

3.1 Surface treatments

Forty-eight SLA surface-treated dental implants (SuperLine 3.6 × 8.0 mm, Dentium, Suwon, Korea) and 48 machined-surface healing abutments (HAB453050E 4.5 × 3.0 mm, Dentium) were prepared. To minimize the influence of the occlusion force, a healing abutment was used instead of the final prosthesis. This is because uncontrolled excessive occlusal force during the healing period can result in fibrous encapsulation of the implants rather than osseointegration.[28] The implants and healing abutments were divided into four groups (n=12 for each group), as follows:

- CON group: SLA implants and machined healing abutments without any additional surface treatments.
- UV group: Implants and healing abutments were treated with UV for 15 min using a UV-

light emitting device (TheraBeam SuperOsseo, Uchio Inc., Tokyo, Japan) before implant placement. The UV was delivered as a mixture of spectra via a single UV lamp at wavelengths of 360 nm and 250 nm.[29]

• AN group: Implants and healing abutments were soaked in 10^{-3} M alendronate (Cayman Chemical, Ann Arbor, MI, USA) for 24 h.

• ANUV group: Implants and healing abutments were treated with alendronate, followed by UV irradiation, with each method adhering to the protocol described above.

3.2 Surgical procedures

Under general and local anesthesia, eight teeth, from the second premolar to the first molar of the mandible were extracted. Following tooth extraction and curettage, the sockets were liberally irrigated with saline and sutured with 3-0 synthetic resorbable materials (Vicryl; Ethicon, Somerville, NJ). After 3 months of healing, implants were placed under the same surgical conditions as those used for tooth extraction. A researcher who was blinded to the groups performed the surgery. Another researcher prepared the four groups of implants with different surface treatments. The implant surgery was performed as follows. An incision was made on the crest of the ridge to create full-thickness buccal and lingual flaps, and the exposed bone was flattened using a ridge contouring bur. In each adult dog, six implants were inserted into the mandible on each side, totaling 12 implants (Figures 1 and 2). Cavities for implant placement were formed with a 2.2-mm guide drill and enlarged

with a 2.85-mm final drill.

To prevent overheating during drilling, the site was continuously irrigated with sterile saline. After implant placement, the flaps were sutured with a 3-0 synthetic resorbable material (Vicryl) using the vertical mattress suture technique. The order of the implants placed in each dog is shown in Table 1. In consideration of the difference in bone quality and the effect of the opposite teeth between the premolar and molar areas, the four groups of implants were evenly distributed.

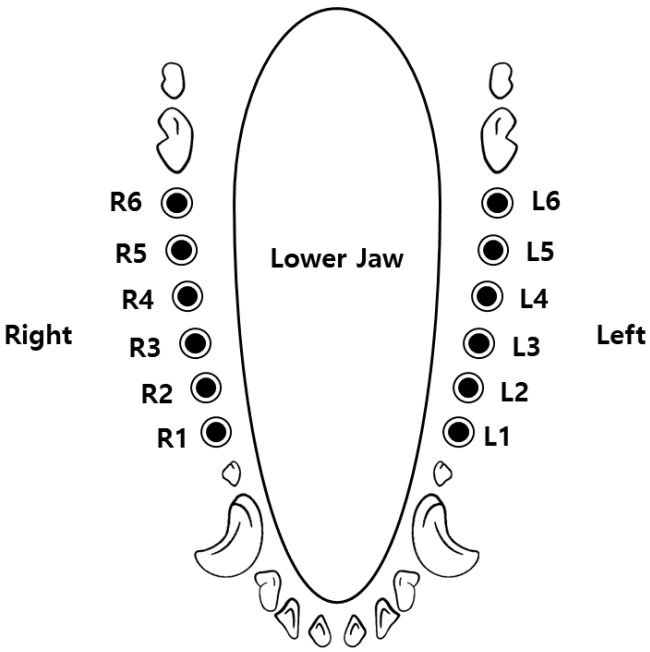

Figure 1. The implantation sites of 12 mandibular implants in a mongrel dog
The sites for implant insertion are labeled R1, R2, R3, R4, R5, and R6 from the anterior part of the right mandibular molars to the ipsilateral posterior part of the molars, and L1, L2, L3, L4, L5, and L6 from the anterior part of the left mandibular molars to the ipsilateral posterior part of the molars.

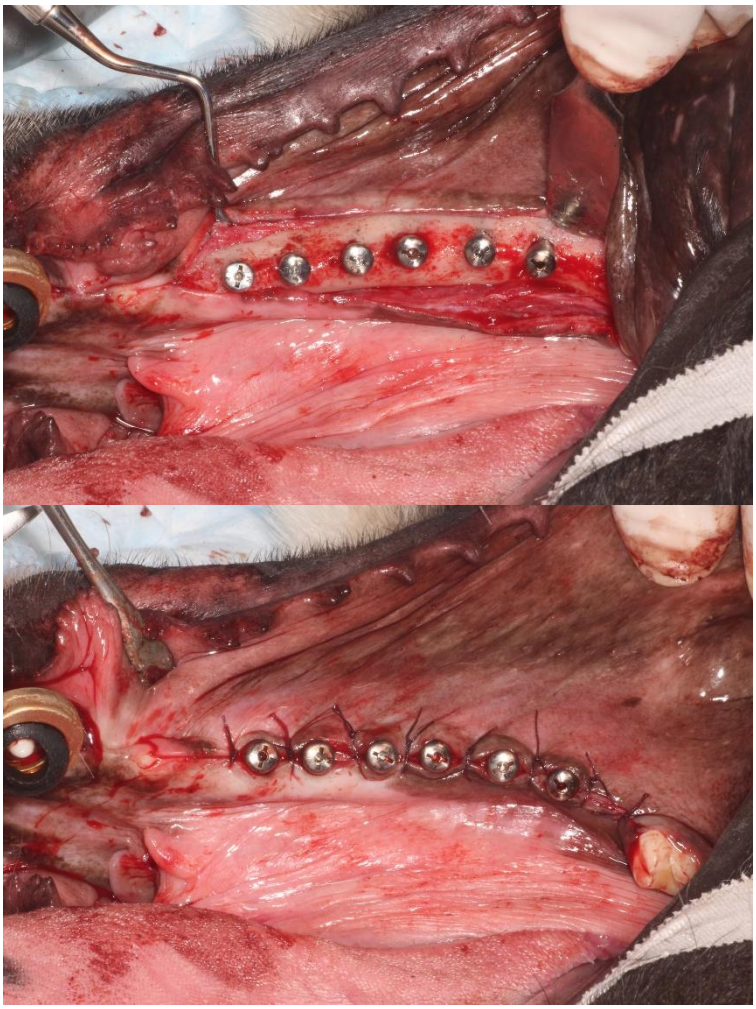

Figure 2. Clinical photograph illustrating the implants placed in the mandible of a mongrel dog

Table 1. Sites of insertion for the four groups of implants

	R6	R5	R4	R3	R2	R1	L1	L2	L3	L4	L5	L6
Dog#1	UV	CON	UV	AN	ANUV	CON	CON	UV	AN	ANUV	CON	UV
Dog#2	AN	UV	AN	ANUV	CON	UV	UV	AN	ANUV	CON	UV	AN
Dog#3	ANUV	AN	ANUV	CON	UV	AN	AN	ANUV	CON	UV	AN	ANUV
Dog#4	CON	ANUV	CON	UV	AN	ANUV	ANUV	CON	UV	AN	ANUV	CON

CON, control group; UV, UV-treated group; AN, alendronate-immersed group; ANUV, alendronate soaking and UV treated group.

Four weeks after implant placement, two mongrel dogs (Dog#2 and Dog#4) were sacrificed for block bone sectioning, which included the insertion site. The samples were fixed in 10% formalin. The dogs were sacrificed as follows. Zolazepam (5 mg/kg; Zoletil, Virbac, Carros, France) was injected intramuscularly to induce sedation, and the animal was moved from the housing room to the preparation room. Then, a catheter was inserted into the cephalic vein, and alfaxalone (3 mg/kg; Alfaxan, Jurox Pty Ltd, Rutherford, NSW, Australia), medetomidine HCl (0.75 mg/kg; Tomidin, Provet, Istanbul, Turkey), acepromazine maleate (0.6 mg/kg; Sedaject, Samu Median, Seoul, Korea), and tramadol HCl (5 mg/kg; Trodon injection, Ajupharm, Seoul, Korea) were injected intravenously. Next, the animals were euthanized by cardiac arrest induced using an intravenous injection of potassium chloride (3 g/20 mL; Potassium Chloride-40 injection, Daihan, Seoul, Korea). At 8 weeks after implant placement, the remaining two dogs (Dog#1 and Dog#3) were also sacrificed in the same manner for block bone sectioning.

4. Sample size

The sample size was determined by referring to the previous study.[12] In this study, the implants were divided into four groups according to the surface treatment methods and a total of 24 implants were used, six in each group. According to the previous study, 12 implants were set up per mongrel dog, and two dogs were needed accordingly. However, in this study, 48 implants and four mongrel dogs were used to analyze the difference between the 4-week and 8-week healing periods. This corresponds to a sample size calculation using the degree of freedom.[30,31]

5. Histological analysis

For histological analysis, resin blocks were prepared using the following process: First, the specimens were fixed in buffered neutral formalin (Sigma Aldrich, St. Louis, Missouri, USA) solution for 2 weeks and dehydrated with increasing concentrations of ethanol. For resin infiltration, the dehydrated tissue specimens were placed in a mixture of ethanol and Technovit 7200 resin (Heraeus Kulzer, Wehrheim, Germany), with an increasing ratio of resin. The infiltrated tissue specimens were embedded in an embedding mold. The specimens were inserted into a UV embedding system (KULZER EXAKT 520, Heraeus Kulzer**,** Norderstedt, Germany) and cured for 1 day.

The desired sections of the cured specimens were sectioned using a diamond cutting system (EXAKT 300 CP, EXAKT Advanced Technologies, Norderstedt, Germany) and attached to slides using an adhesive press system. The final slides were ground to a

thickness of 40±5 μm using an EXAKT grinding system (KULZER EXAKT 400CS, EXAKT Advanced Technologies, Norderstedt, Germany). Of these, the two most central sections of the implant were selected. One section was stained with hematoxylin and eosin and the other was stained with Goldner's trichrome to visualize the CTA to the healing abutment. Histological examination was performed using a light microscope (DMR; Leica, Nussloch, Germany), and quantitative analysis was performed using computer software (CaseViewer version 2.1, 3DHisTech, Budapest, Hungary; ImageJ, National Institutes of Health, Bethesda, Maryland, USA). Considering previous studies, the osseointegration of implants was evaluated by measuring the BIC (%)[2,11,12,15,32] and bone density (BD, %).[12,32,33] The BIC and BD were measured separately in the cortical bone and cancellous bone areas (Figure 3). The mucosal attachment was also evaluated by measuring the CTA (μm).[20,21,34] The measurements were defined as follows:

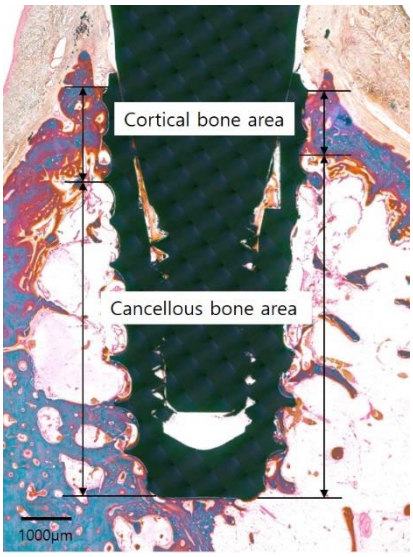

Figure 3. Bone segmentation for histomorphometry

(1) BIC (%): The percentage of the bone-to-implant contact length with respect to the implant surface length (Figure 4).

(2) BD (%): The percentage of the bone area to the total area within a 500 μm-wide zone lateral to the implant between the uppermost thread and bottommost thread in the cortical

bone and cancellous bone areas (Figure 4).

(3) CTA (μm): The length from the apical end of the junctional epithelium to the fixture-abutment connection, that is, the length of the connective tissue attached to the healing abutment (Figure 5).

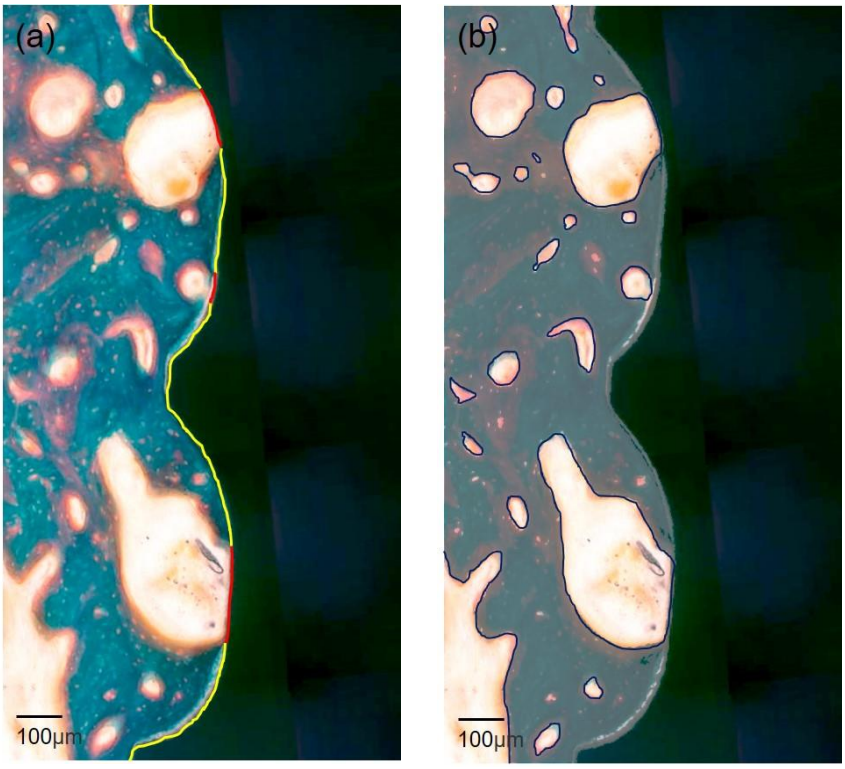

Figure 4. Measurement of the bone-to-implant contact and bone density
(a) BIC (%) is the percentage of the bone-to-implant contact length (yellow lines) with respect to the implant surface length (yellow and red lines). **(b)** BD (%) is the percentage of the bone area (grey area) to the total area within a 500 μm-wide zone lateral to the implant. Only the two threads of the implant are shown for simplicity.

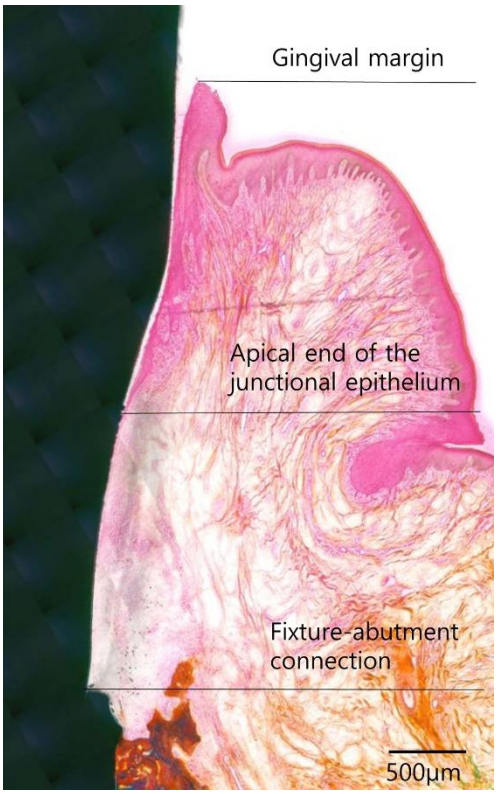

Figure 5. Connective tissue attachment measurement

The failed implants were planned to be excluded from the analysis. The following conditions were considered implant failures[35]: (1) horizontal and/or vertical mobility, (2) uncontrolled progressive bone loss, (3) uncontrolled exudate, or (4) more than 50% bone loss around the implant. In addition, when measuring the CTA, areas with a deep or shallow implant placement depth on the crestal bone level were excluded from the measurement. In other words, CTA was measured only in the area where the implant was placed with an equicrestal position.

6. Statistical analysis

Data were analyzed using statistical software (SPSS Statistics version 25.0; IBM Corp., Armonk, NY, USA). One-way analysis of variance followed by a post-hoc least significant difference test was used to identify the effects of UV treatment, alendronate, and the different healing periods. The level of significance was set at $\alpha=0.05$.

III. Results

1. Histology

Low-magnification histological images showing the entire implant parts were examined. These images were representative images of each group. Overall, there were no large differences in bone density between the CON, UV, AN, and ANUV groups (Figure 6).

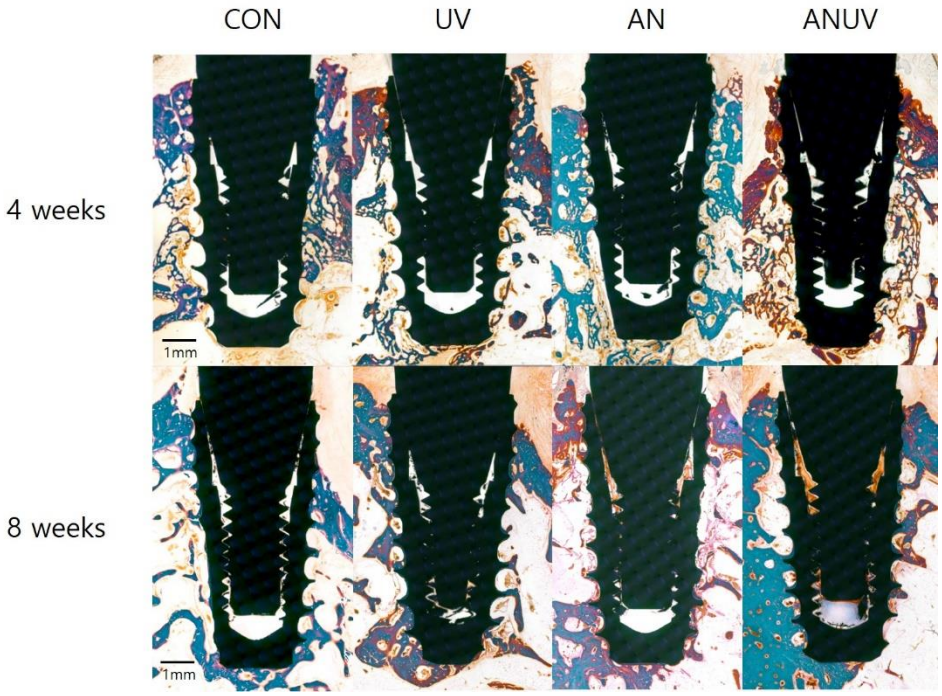

Figure 6. Low-magnification histologic photomicrographs, taken at 4 and 8 weeks
CON, control group; UV, UV-treated group; AN, alendronate-immersed group; ANUV, alendronate soaking, and UV treated group (Goldner's trichrome).

The higher-magnification histological images also did not reveal notable differences in bone density between the groups. However, a greater bone and implant surface contact was observed in the cortical bone area in the UV and ANUV groups. In contrast, no notable differences were found in the cancellous bone area between the groups (Figure 7).

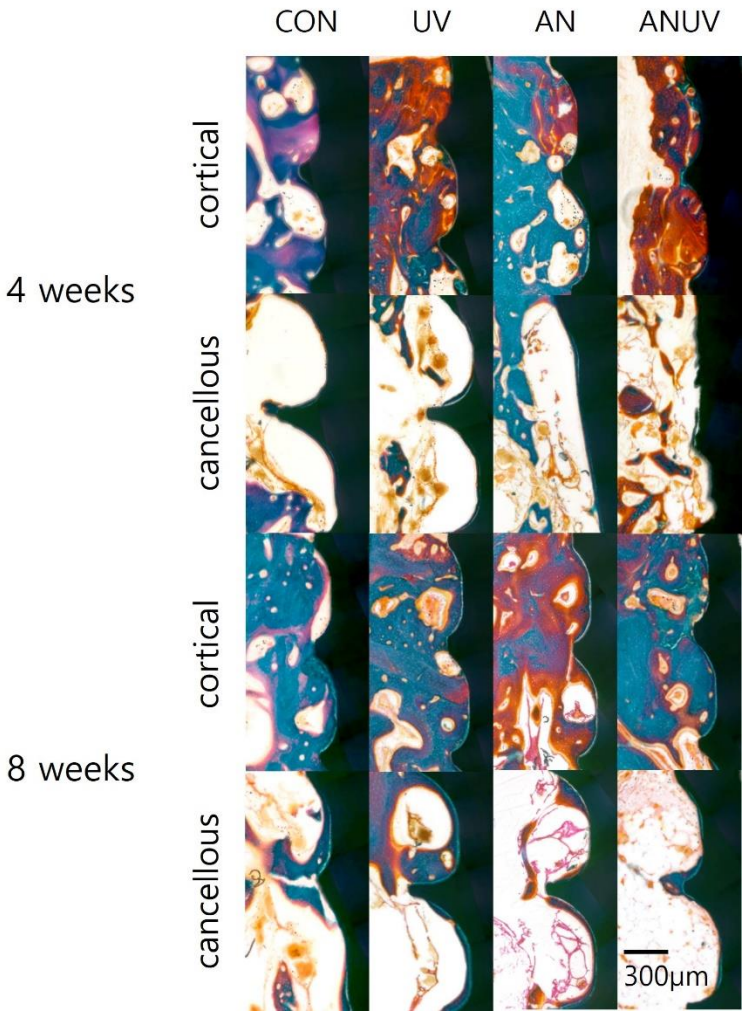

Figure 7. High-magnification histologic photomicrographs, taken at 4 and 8 weeks

These are high-magnification histologic photomicrographs of the region that are representative of each group. The bone tissue is stained blue and orange. CON, control group; UV, UV-treated group; AN, alendronate-immersed group; ANUV, alendronate soaking and UV treated group (Goldner's trichrome).

2. Histomorphometrical evaluation

Since there were no failed implants, all implants were used for measurement without exclusion. However, due to problems with implant placement depth, one sample from each of the groups at 4 weeks and the ANUV group at 8 weeks was excluded, and a smaller number of samples were used for the analysis of CTA. In the cortical bone, BIC was significantly increased in the UV treatment group compared with that in the CON and AN groups at 4 weeks (CON [78.69±8.48%] vs. UV [88.37±5.20%], p=.047; UV [88.37±5.20%] vs. AN [76.69±8.22%], p=.019) and 8 weeks (CON [82.96±7.02%] vs. UV [91.99±6.21%], p=.028; UV [91.99±6.21%] vs. AN [82.64±7.47%], p=.024) (Table 2). In contrast, alendronate-only treatment and UV-alendronate combined treatment did not significantly increase the BIC. In cancellous bone, none of the treatments had any effects, and no significant difference was found with respect to the healing periods (Figure 8).

Table 2. Descriptive statistics of the BIC and BD values by groups and healing periods

	Period/Group	BIC (%)				BD (%)			
Cortical	4 weeks	Mean ± SD	Min	Med	Max	Mean ± SD	Min	Med	Max
	CON	78.7 ± 8.5	62.7	81.8	86.1	80.5 ± 10.2	67.5	82.4	93.4
	UV	88.4 ± 5.2	81.8	90.4	92.9	75.2 ± 6.8	69.1	71.9	85.2
	AN	76.7 ± 8.2	64.1	75.9	89.4	72.0 ± 8.4	58.5	75.1	80.6
	ANUV	85.3 ± 9.2	70.1	86.0	97.4	78.4 ± 7.2	70.2	77.9	91.4
	8 weeks	Mean ± SD	Min	Med	Max	Mean ± SD	Min	Med	Max
	CON	83.0 ± 7.0	74.4	82.1	92.2	80.7 ± 6.7	71.6	83.4	86.8
	UV	92.0 ± 6.2	81.0	93.5	99.2	81.1 ± 3.9	73.6	81.7	84.5
	AN	82.6 ± 7.5	75.0	81.7	93.4	82.0 ± 9.5	70.7	84.4	94.1
	ANUV	90.3 ± 5.6	81.2	93.1	94.7	80.3 ± 12.0	66.2	81.9	95.2
Cancellous	4 weeks	Mean ± SD	Min	Med	Max	Mean ± SD	Min	Med	Max
	CON	57.5 ± 15.9	41.7	53.3	79.2	34.1 ± 13.8	19.4	30.1	57.6
	UV	66.4 ± 7.6	58.2	65.7	75.5	35.4 ± 17.8	14.5	32.3	64.9
	AN	67.6 ± 14.2	45.9	68.1	82.9	36.9 ± 7.6	28.0	36.3	48.8
	ANUV	63.0 ± 16.1	36.0	65.8	79.4	33.7 ± 7.6	25.2	33.4	46.2
	8 weeks	Mean ± SD	Min	Med	Max	Mean ± SD	Min	Med	Max
	CON	58.4 ± 15.0	40.8	58.8	75.7	30.3 ± 9.0	16.7	30.4	43.1
	UV	66.5 ± 15.4	38.5	67.7	82.0	29.8 ± 6.9	21.9	30.4	37.6
	AN	57.4 ± 17.5	32.9	58.2	81.5	25.5 ± 9.6	17.1	22.3	42.0
	ANUV	48.5 ± 25.5	16.8	48.0	79.2	26.1 ± 7.7	16.8	23.6	37.6

Abbreviations: BIC, bone-to-implant contact; BD, bone density; SD, standard deviation; Min, minimum; Med, median; Max, maximum. Data are expressed as mean ± standard deviations and rounded to the first decimal place.

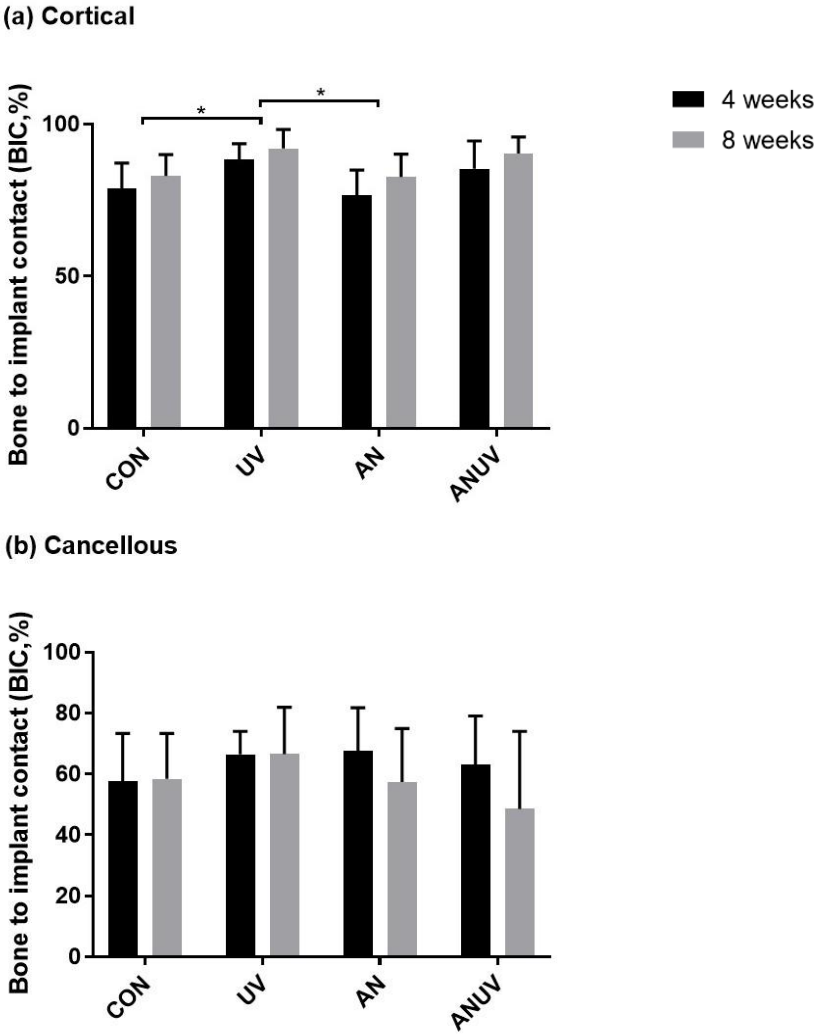

Figure 8. The bone to implant contact (BIC, %) at 4 weeks and 8 weeks of healing
The BIC was evaluated in the cortical (a) and cancellous (b) bone areas. CON, control group; UV, UV-treated group; AN, alendronate-immersed group; ANUV, alendronate soaking and UV treated group. *P<0.05.

With respect to BD, none of the treatments showed a significant increase. In the AN group, BD of the cancellous bone was significantly lower after 8 weeks of healing than after 4 weeks of healing (4 weeks [36.94±7.56%] vs. 8 weeks [25.47% ±9.61%], p=.044) (Table 2, Figure 9). No significant differences in the CTA were found between the groups, and although the values generally increased with an increasing healing period, the differences were not statistically significant (Table 3, Figure 10).

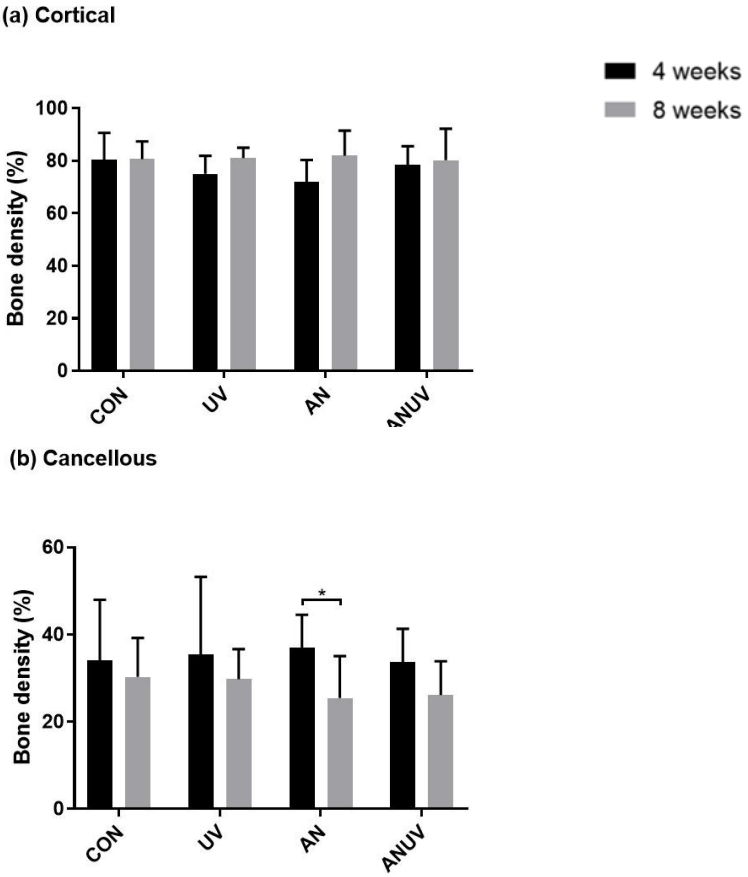

Figure 9. Bone density (%) at 4 and 8 weeks of healing

CON, control group; UV, UV-treated group; AN, alendronate-immersed group; ANUV, alendronate soaking and UV treated group. *P<0.05.

Table 3. Descriptive statistics of the CTA values by groups and healing periods

Period/ Group	CTA (μm)							
	4 weeks				8 weeks			
	Mean ± SD	Min	Med	Max	Mean ± SD	Min	Med	Max
CON	2274.3 ± 1375.7	343.7	2297.9	4099.6	2811.0 ± 615.0	1862.4	2822.7	3679.2
UV	2704.3 ± 1544.9	253.4	2957.7	4023.7	2200.9 ± 1140.0	718.5	2229.4	3461.0
AN	2411.8 ± 1207.3	624.9	2442.3	3669.1	2866.0 ± 722.1	1772.3	3108.1	3665.0
ANUV	2476.4 ± 1175.3	794.6	2805.6	3845.8	2180.2 ± 704.9	1486.2	1978.7	3345.4

Abbreviations: CTA, connective tissue attachment; SD, standard deviation; Min, minimum; Med, median; Max, maximum. Data are expressed as mean ± standard deviations and rounded to the first decimal place.

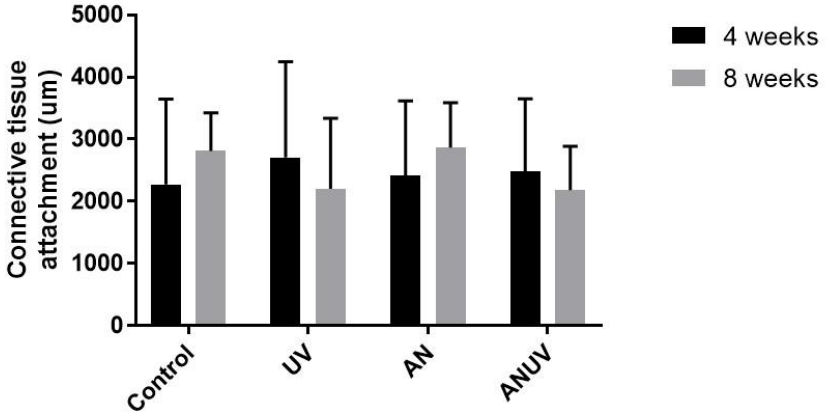

Figure 10. The connective tissue attachment (μm) at 4 and 8 weeks of healing
CON, control group; UV, UV-treated group; AN, alendronate-immersed group; ANUV, alendronate soaking and UV treated group.

IV. Discussion

In the cortical bone, UV treatment significantly increased the BIC. These UV effects were reported in previous studies. The UV irradiation photochemical modification of the oxide layer on the surface of titanium dental implants and the titanium dioxide surface, increases hydrophilicity, enhances osteogenic differentiation, and promotes hard tissue integration.[36,37] This is because UV irradiation removes hydrocarbons on the titanium dioxide surface to create a hydrophilic environment.[38] An *in vivo* experiment also reported the beneficial effects of UV treatment of SLA-treated implants on bone seal around the marginal-to-transcortical area, which led to better bone coverage.[32]

In contrast, none of the treatment options had a significant effect on the BIC in the cancellous bone area. The osseointegration of dental implants can be described as two different osteogenesis phenomena.[39] Distance osteogenesis is an appositional bone growth that occurs from the existing peri-implant bone toward the implant surface. Contact osteogenesis is de novo bone formation that occurs from the implant surface toward the bone, which is influenced by the surface designs and characteristics of the implants. The increase in BIC by UV treatment is related to contact osteogenesis. An important aspect of contact osteogenesis is the recruitment of osteogenic cells and their migration to the implant surface. In other words, osteoconduction is an important factor for contact osteogenesis. However, since the bone density of the cancellous bone is very low, osteoconduction occurs

less in the cancellous bone than in the cortical bone. This may be the reason why UV treatment in the cancellous bone did not provide a significant effect. Despite the lack of effects in the cancellous bone, an increased BIC in the cortical bone by UV treatment has clinical significance because the cortical bone plays an important role in the primary stability of implants.[40] In particular, this may be more important for short implants, or immediate implant placement that is unfavorable to primary stability.[41,42]

Based on a previous cell-level study, the method of soaking implants in 10^{-3}M alendronate for 24 hours was used in this study.[27] However, this treatment did not show a statistically significant effect on the increase in bone formation in terms of BIC and bone density. Our results are consistent with the findings of some previous studies that reported that local zoledronate applications were ineffective in enhancing the bone adhesion of implants.[43,44] In contrast, several other studies have reported that the use of local alendronate improved implant osseointegration, but the treatment concentration of alendronate and the loading method of alendronate on the surface of the implant was different.[19,20,45,46] The reported methods include a Ca-P-coating method, in which alendronate is loaded onto the surfaces,[19] the creation of a crosslinked fibrinogen binding layer,[45] and soaking SLA implants in alendronate without pretreatment.[46] The bisphosphonate treatment concentrations were also different, at 10^{-6} M alendronate [46] and 10^{-2} M alendronate.[18] Of these, the method of soaking SLA implants in alendronate did not show any significant effects even though a higher alendronate concentration (10^{-3} M) was used in the present study. This indicates that there is a need for further research to identify adequate methods for alendronate loading on

implant surfaces and the most effective alendronate treatment concentration.

SLA implants were used as a control group in the present study because SLA is the current surface treatment of choice. However, some previous studies have used stainless steel screws etched with concentrated HF with an immobilized fibrinogen layer as a control instead of an SLA surface, and compared them to screws with immobilized bisphosphonate on the fibrinogen layer to assess the effects of bisphosphonate.[33,45] Therefore, different results may arise depending on the type of implant surface used as a control. In the present study, the SLA surface, which already has sufficient osseointegration capacity, was used as a control, and the implants were inserted into the bones with sufficient healing, which may explain why no effects were found with the use of bisphosphonate. A previous study examined the effects of hydroxyapatite coating and alendronate soaking of titanium-machined-polished implants on peri-implant defect regeneration with the implants inserted immediately after extraction. The authors found that alendronate treatment was effective in increasing the early bone formation rate.[17] This result suggests that the use of bisphosphonate to improve osseointegration of implants may be more valuable in poor bone conditions such as bone defects than in ideal conditions.

It is well recognized that systemically administered bisphosphonate-based drugs, such as alendronate, may have side effects including bisphosphonate-related osteonecrosis of the jaw (BRONJ or MRONJ).[47-49] Moreover, it has been reported that BRONJ prevalence increases with increasing dosages of bisphosphonate-based drugs.[50,51] Hence, if the dose of the drug used is reduced, the side effect can also be reduced. Local injection can limit the

drug to a small amount and target the amount to the surroundings of the implant. Furthermore, when alendronate is applied indirectly by soaking the implant in alendronate, as in this study, a smaller amount of the drug will act locally. Therefore, the side effect will also be lowered. A previous study in a rat model reported that local bisphosphonate treatment is less likely to induce osteonecrosis of the jaw than systemic treatment.[52] Additionally, the bisphosphonate treatment duration is an important factor in BRONJ development. The longer the bisphosphonate administration period, the higher risk of BRONJ.[51,53] Since alendronate was applied locally on a one-time basis, the possibility of complication is considered very low in this study. More research on the long-term effects of various local application methods of alendronate is necessary.

There was no synergistic effect in bone formation from the use of alendronate and UV. These results were different from those of Kim et al. In their study, a synergy effect was detected in the rabbit model.[46] However, in the study of Kim et al., the treatment order of alendronate and UV was not specified. In most previous studies that examined the effect of UV treatment, UV treatment was performed at the chairside before implant placement.[54,55] Interestingly, even after UV irradiation, titanium aging occurs, which changes the titanium surface from hydrophilic to hydrophobic due to the progressive accumulation of hydrocarbons under ambient conditions.[56] In another study, it was reported that the effect of UV treatment only lasted a few minutes in ambient air at room temperature.[57] In the present study, alendronate soaking was required for 24 hours, thus, alendronate treatment was performed first. This is in line with previous studies. Subsequently, UV treatment was

performed immediately before implant placement at the chairside. However, this order may have influenced the results of the group treated by both alendronate and UV. This is because alendronate, an organic compound, can be destroyed by the radical reaction of UV irradiation.[58] Therefore, the effects of alendronate soaking and UV treatment seem incompatible. However, a previous study at the cell level reported that prior UV treatment was helpful in loading more alendronate to the implant surface.[27] Another study also reported that the surface characteristics produced by UV irradiation were maintained for 28 days when the titanium discs were stored in distilled H2O after UV treatment.[56] This result suggests that the effect of UV treatment may be maintained even after alendronate soaking. Therefore, a follow-up study at the *in vivo* level is needed to see if there is a synergistic effect when the implant is immersed in alendronate after UV treatment first by changing the surface treatment order.

In this study, no remarkable effects on mucosal attachment to the healing abutment (machined surface) were found following UV and alendronate treatments. An *in vitro* study reported that increasing the hydrophilicity of titanium dioxide-coated surface with UV treatment (wavelength 368 nm, 3.8 W, 24 h) markedly increased the initial response of human fibroblasts.[59] Conversely, another study found that UV treatment (wavelength 254 nm, 36 W, 15 min) of the titanium surface increased wettability, but did not significantly increase human gingival fibroblast attachment.[60] Importantly, in that study, UV treatment was administered for 15 min, and the authors stated that there is a need to find an optimal UV treatment time to ensure a biological response. In the present study, 15 min of a mixed

spectrum of 360 and 250 nm wavelengths was used for UV treatment. Since consensus is lacking, there is a need to identify the optimal UV treatment conditions using animal and cellular experimental models.

Moreover, the effects of UV and alendronate treatment on bone healing were assessed at 4 weeks and 8 weeks after implantation. The length of these periods was thought to be long enough for soft tissue healing. Indeed, one study examined the early healing of implants placed into fresh extraction sockets at 1, 2, 4, and 8 weeks after implantation and found an absence of inflammation, complete maturation of the epithelium, and the presence of dense and connective tissues at 4 and 8 weeks.[34] In the future, more research studies to investigate early soft tissue healing are warranted.

Regarding the effects of alendronate on mucosal attachment, a previous *in vitro* study reported that both alendronate treatment and UV-alendronate combined treatment of the machined surface showed no effects on fibroblasts.[27] In the present study, we examined the effects of different surface treatments in mongrel dogs, and we did not find an increased mucosal attachment of the machined-surface abutment using alendronate treatment.

This study has several limitation. First, the central section of the implant was selected after sectioning of the tissue specimen to measure bone formation and mucosal attachment, but the procedure did not reflect both the three-dimensional bone volume and mucosal attachment around the implants. Second, the healing period was predetermined at 4 and 8 weeks, based on previous studies that observed implant osseointegration in dog models for various purposes.[7,18,61,62] However, as mentioned before, a period of 4 to 8 weeks after

implant placement may be long enough for soft tissue healing in a dog model.[34] Hence, in this present study, the initial soft tissue healing effect according to the surface treatment of the abutment may have been masked. Since the number of samples in each group was also small, the results of this study should be interpreted with caution.

V. Conclusion

UV treatment of implants significantly increased the BIC in the cortical bone area. However, UV treatment did not affect the cancellous bone area and there was no significant increase in bone density. Alendronate treatment did not enhance the BIC or bone density, and there was no synergistic effect when combined with UV irradiation. Furthermore, UV and/or alendronate treatment did not significantly increase the CTA.

Despite the limitations of an animal study with a limited number of implants, our observations led to the following conclusions. Concerning the BIC, UV treatment enhanced the osseointegration of implants. However, these effects were limited to the cortical bone area, and no significant effect was found in the cancellous bone area. Alendronate treatment did not have any significant effect on the enhancement of osseointegration. Further research is necessary to determine the effective methods for loading alendronate on implant surfaces. When implants were treated with alendronate, followed by UV irradiation, there was no synergistic effect on osseointegration. Moreover, alendronate and UV treatments did not significantly improve tissue healing in terms of mucosal attachment. Further research studies to examine their effects of soft tissue healing under various UV treatment conditions and healing periods are necessary.

The null hypothesis of this study was rejected in terms of osseointegration because bone formation improvement in UV-treated groups was observed *in vivo*. However, there was

no difference in mucosal attachment in any of the groups, so the null hypothesis was not rejected for mucosal attachment.

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ABSTRACT (Korean)

자외선 조사 및 알렌드로네이트 침지를 이용한 표면처리가 치과 임플란트의 골유착과 점막부착에 미치는 영향

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본 연구의 목적은 자외선(ultraviolet, UV)조사와 알렌드로네이트(alendronate) 침지를 이용한 표면처리가 치과 임플란트의 골유착과 치과 임플란트 지대주의 점막부착에 미치는 영향을 알아보는 것이다. 이를 위해, 48개의 SLA(sandblasted, large-grit, acid-etched) 티타늄 임플란트와 48개의 machined surface 치유 지대주 그리고 4마리의 잡견이 이용되었다. 임플란트와 치유지대주는 표면처리 방법에 따라 각각 네 가지 그룹으로 분류하였다(각 그룹당 n=12). 대조군은 어떠한 표면처리도 하지 않았다. UV 그룹은 15분간 자외선 조사를 시행하였으며, AN 그룹은 10^{-3} M

알렌드로네이트에 24시간동안 침지 시켰다. ANUV 그룹은 알렌드로네이트 침지 후 자외선조사를 시행하였다. 모든 임플란트는 잡견의 하악골에 식립되었으며, 실험동물은 술 후 4주와 8주에 희생되었다. 이후 골과 임플란트 접촉(bone to implant contact, BIC), 골밀도(bone density, BD) 그리고 결합조직부착(connective tissue attachment, CTA)을 측정하였다. 실험결과, 자외선 조사는 피질골부위에서 SLA임플란트의 BIC을 유의미하게 증가시켰다. 하지만 알렌드로네이트 침지는 BIC와 골밀도를 유의미하게 증가시키지 못하였으며, 자외선 조사와 시너지효과도 없었다. 또한 자외선 조사 및 알렌드로네이트 침지 모두 machined surface 치유 지대주의 결합조직 부착을 유의미하게 증가시키지 못하였다. 이상의 결과에 따라 SLA 티타늄 임플란트에 대한 자외선 조사는 임플란트의 골유착을 촉진하지만 알렌드로네이트 침지는 효과가 없으며, 지대주에 대한 자외선 조사와 알렌드로네이트 침지 또한 점막부착에 별다른 효과가 없다고 결론지을 수 있다.

핵심 되는 말: 알렌드로네이트, 결합조직부착, 치과 임플란트, 치과 임플란트 지대주, 골유착, 자외선