이학석사 학위논문

# Quantification of volumetric absorption for absorbable implant using micro-CT

# Micro-CT를 이용한 흡수성 임플란트의 체적 흡수율 정량화

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서울대학교 대학원

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A thesis of the Degree of Mater of Science

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Interdisciplinary Program in Radiation
Applied Life Science,
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# Quantification of volumetric absorption for absorbable implant using micro-CT

by
Sung Won Kang

A Thesis Submitted to the Interdisciplinary Program in Radiation Applied Life Science in partial fulfillment of the requirement of the Degree of Master of Science in Seoul National University College of Medicine

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# ABSTRACT

**Introduction:** The purpose of the study was to quantify the VA (volumetric absorption) from the result of osseointegration in micro-CT analysis. We have developed a new method to evaluate the osseointegration and absorption of the absorbable implant using micro-CT images. The measurement was correlated with the histomorphometric analysis.

**Methods:** For the procedure, mandibular 2 and 4 premolars were extracted bilaterally from seven experimental dogs (beagle dog), and installed two PLA-TCP 30% implants on each side.

For close examination, the implants with its surrounding tissue were dissected to safely remove implants from the figures in sequence of 4 week, 8 week, and 12 weeks lapse since the installation. Seven implants were damaged and excluded and total 21 implants samples were used for the analysis.

From the Micro- CT scan images, the confidence connected segmentation, connected threshold segmentation, morphology operation and labeling algorithm were applied, and volumetric analysis was performed between bone and implant to measure the VBIC (Volumetric Bone-Implant contact) and VA(Volumetric Absorption). The implant slices were prepared by dissecting the center area of the sample tissues in axial direction for histomorphometric analysis of BIC (Bone-Implant contact) and BA (Bone Area).

**Results:** As a result, the mean of VA and VBIC increased significantly with an increase in the healing period ($p<.01$ ANOVA, $p<0.05$ the turkey's multiple comparison test)
The BA and the BIC did increase over the implant installation time period, but the difference of mean did not show significant difference. After analyzing the correlation between the VBIC and the VA based on Micro-CT analysis (which showed significant difference previously), it showed significant difference in correlation 0.463.

**Conclusions:** A compare of two different methods for quantify of osseointegration, histomorphometric analysis was limited to the absorbable implant analysis because the absorbable implant change in the size. In contrast, VA of absorbable implant showed significant correlation with VBIC, and it has provided a new parameter for osseointegration evaluation. Therefore, quantification of VA is required to evaluate osseointegrationun of an absorbable implant besides the other existing methods.

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Keywords: Absorbable implant, Implant absorption, bone implant contact, Bone area, Histomorphometry, micro-CT
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# INTRODUCTION

The dental implant treatment procedure for adult patients is extensively used in clinics recently. Surface characteristics and biocompatibility of implant materials are reported as the most important elements in successful osseointegration [1]. Titanium is the common material used for existing implants for their outstanding osseointegration.

The installation of implant with non-absorbable material for treatment of children still in their growth period can lead to its lower sedimentation caused by the growth surrounding alveolar bone [2]. The ankylosed implant inhibited the alveolar bone immediately preventing it from undergoing the growth occurring elsewhere in the jaws [3].

Currently, there is no proper implant treatment method available for replacement of the deciduous tooth loss in pediatric dentistry. We have been developing implant of absorbable material that can be absorbed even in case of sedimentation during growth period. The implants of bioabsorbable ceramics have been already used in the orthopedics. The tricalcium phosphate (TCP) becomes a part of bone after being absorbed [4].

The polylactic acid (PLA) used in orthopedics has been reported to induce over 50% regeneration of bone loss region [5, 6]. Other synthetic biodegradable materials such as polygycolic acid (PGA) and polycaprolactone (PCL) have property of chemically decomposition in a biological body. To minimize sedimentation of the implant during the growth period, we have been developing a hybrid type implant consisting of the upper part with titanium and the lower part with PLA−TCP.

The osseointegration is critical to the success of dental implant treatment and has been well established with continuous research and development [7, 8]. The osseointegration evaluation for implant of non−absorbable material has been studied continuously [9−12].

histomorphometric analysis to examine thin specimen is used widely for its advantage of high spatial resolution and contrast [13, 14]. The bone−implant contact (BIC) and bone area (BA) has been measured quantitatively to evaluate the osseointegration of non−absorbable implant. The evaluation of osseointegration with this analysis has disadvantages of requiring complex equipment and procedure in preparing thin and dyed specimen. The reproduction of specimen is difficult because of its rather destructive process of making specimen. To overcome these limitations of histomorphometric analysis, volumetric analysis method using micro−CT images has been developed [15−18]. The results of micro−CT and histomorphometric analysis have been reported to have significant correlation [19−21].

The absorbable implant consists of materials of different characteristics with conventional implants and shows morphological change of the implant body itself by absorption during treatment. So, it is difficult to apply previous methods directly to evaluating osseointegration of the absorbable implant. New analysis method is necessary to measure osseointegration of the absorbable implant and to estimate the success rate of the implant. In this study, we have developed a new method to evaluate the osseointegration and absorption of the absorbable implant using a micro−CT image. The evaluation result of the implant was correlated with the histomorphometric analysis.

# MATERIALS AND METHODS

The absorbable implant used in this study is a hybrid type implant (Fig.1). The upper part was manufactured with titanium and the lower part, PLA-TCP. The upper part had a mini implant shape of 5mm length and 3.5mm diameter.

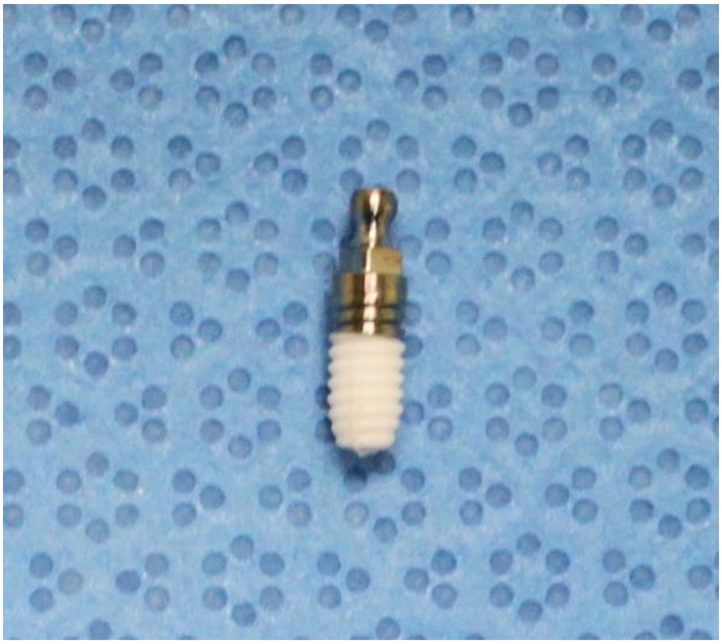

Figure 1. Absorbable implant. Upper part of the implant is consist of titanium and lower part is consist of PLA-TCP 30%(polylactic acid - tricalcium phosphate 30%).

The PLA-TCP 30% hybrid nano-powders were melted into nano-composites to compose implant substructures. In our previous experiment by histomorphometric analysis, the bone area of the absorable implant of TCP 30% was larger than that of any other implants of the TCP 10%, 20%, 40% and 50%.

Seven Beagle dogs (average age of 2 years and weight of 13 kg) were chosen as experimental animals. The Xylazine Hydrochloride (Rumpen, Bayer Korea, Seoul, Korea) mixed with Ketamine (Ketalar, Yuhan, Seoul, Korea) was injected in veins and the second and the fourth premolars were extracted in the left and right lower jaw. A total of 28 implants were placed three months after extraction for alveolar bones to recover (Fig.2).

**Figure 2. Absorbable implant installation in the left and right (2, 4) mandible. Seven beagle dogs were used as experimental animals.**

Seven implants were broken during the placement and excluded from the subsequent experiment. The animals were sacrificed at four, eight and twelve weeks after implant placement. The bones including the implant were cut to achieve samples, which were fixed in 10% formalin solution for 48 hours.

The obtained samples were scanned using a micro−CT, Skyscan 1172 (Skyscan, Konitch, Belgium), at 70kVp and 141μA. The micro−CT image has a pixel size of 9.86μm and 12 bit depth. A non−placed implant was also scanned additionally for using as a control data for comparison (Table 1).

**Table 1.** Values of micro−CT parameter

| | Pre−set value |
|---|---|
| Filter | Al 0.5 mm |
| Resolution | 9.8 μm |
| Source Voltage | 70 kV |
| Source Current | 141 uA |
| Exposure | 590 ms |
| Rotation Step | 0.400 deg |

A non−placed implant was also scanned additionally as a control image for comparison. Each mandibular premolar of the experiment animals were scan by micro−CT 4 times each session. Non−planted implants were additionally scanned for usage of control group data comparison with experimental groups (Fig. 3).

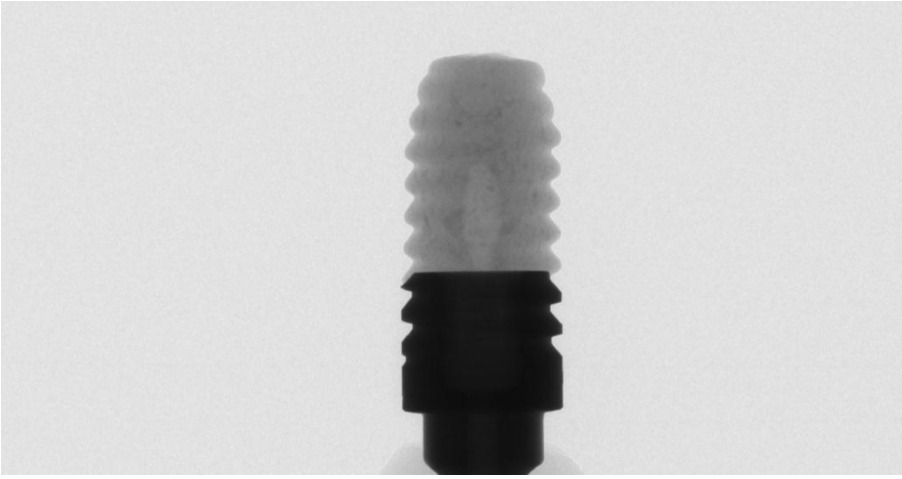
**Figure 3. Absorbable implant radiograph**

All micro-CT images were processed to separate the bone area from the implant area for volumetric analysis of osseointegration. Fig. 4 gives an image processing for volumetric analysis of implants.

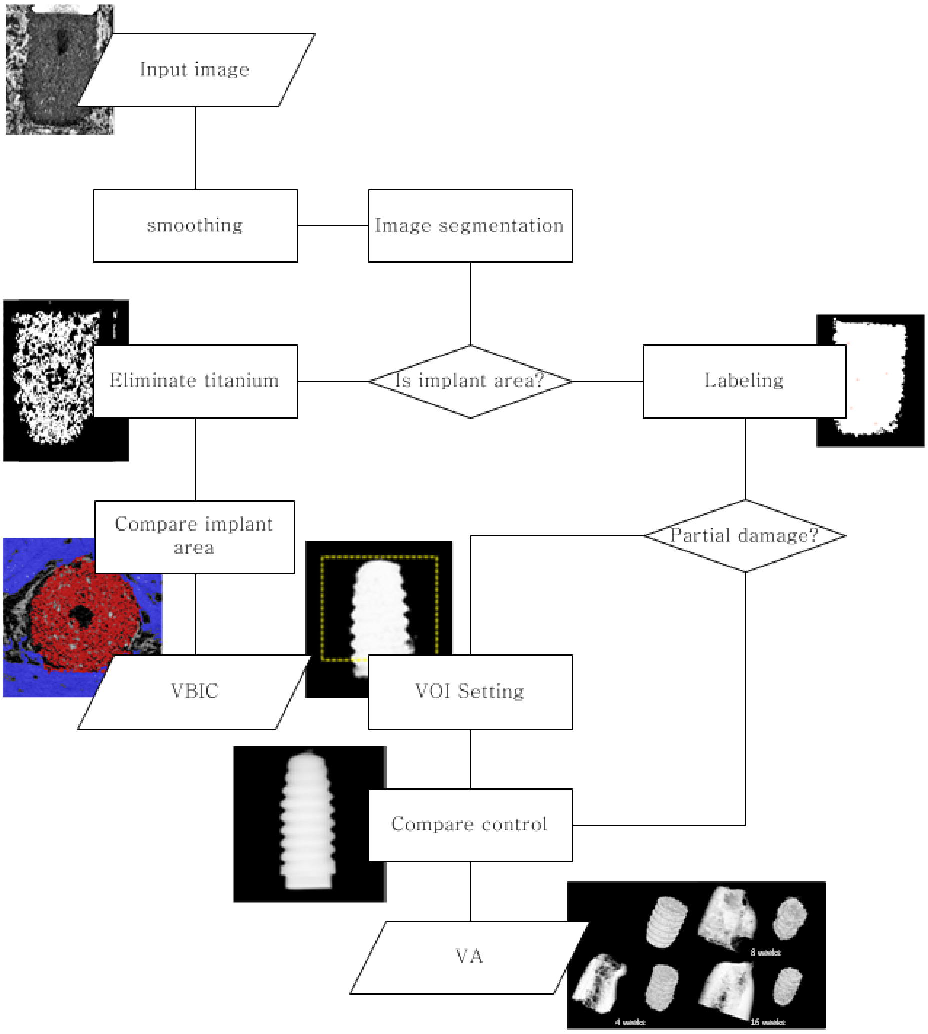


**Figure 4. Image processing for quantification of volumetric absorption and VBIC in micro-CT analysis**

Micro-CT images were processed to separate the implant area from the bone area for three-dimensional (3D) quantitative analysis of osseointegration. The reconstructed image passed through smoothing process using a curvature flow filter to reduce influence of noises of noise (Fig.5a). The bone and implant areas were segmented using an region-based confidence connected segmentation method [22]. First, the bone area was segmented using the segmentation method (Fig.5b). When segmenting the implant area, the holes were generated inside the implant area as the seed boundary values of the segmentation did not include the TCP particles of higher brightness than the normal (Fig.5c). The holes were filled through the additional process of a region labeling method (Fig.5d) [23].

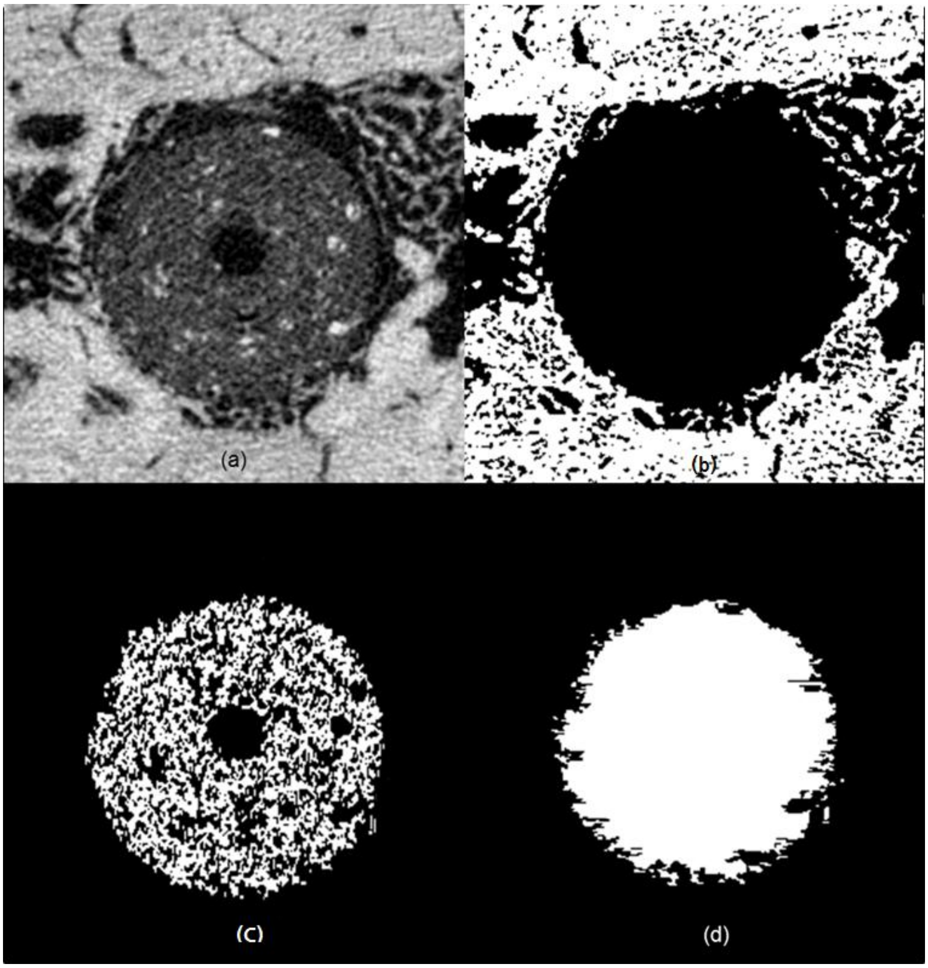

Figure 5. The result of bone and implant segmentation (a) axial image slice (b) The result of confidence connected segmentation of bone (c) The result of confidence connected segmentation of implant (d) The result of implant area after labeling. (4 weeks left side mandibular 2nd premolar, VBIC: 16.38%, VA: 24.12%)

The boundary areas were segmented using morphological operations of erosion and dilation. The segmented areas for the bone and implant were reconstructed three-dimensionally after all the image processing was applied to axial slices of the CT images.

The volumetric absorption (VA) of the implant was calculated by comparison with the volume of a reference implant not placed (Eq.1). The volumetric bone-implant contact ratio (VBIC) was defined as the area of implant surface boundary in direct contact with the bone to the total area of implant surface (Eq.2, Fig.6). All the parameters were measured only for the volume of the lower absorbable implant after excluding the upper titanium.

$$VA = \left(1 - \frac{V_{imp}}{V_{ref}}\right) \times 100 \text{ -------(1)}$$

$V_{ref}$ : *the total volume of reference implant not placed*

$V_{imp}$ : *the total volume of implant placed*

$$VBIC = \left(\frac{S_{bone}}{S_{imp}}\right) \times 100 \text{ ------(2)}$$

$S_{bone}$ : *the area of implant surface in contact with bone*

$S_{imp}$ : *the total area of implant surface*

**Figure 6. Bone−implant contact area. (4 weeks left side mandibular 2nd premolar, VBIC: 16.38%)**

The samples were also made into slices for 2D histomorphometric analysis. Two−dimensional optical images of the slices were observed and recorded at magnification of 100X using an optical microscope (BH−2TM, Olympus Optical, Osaka, Japan) (Fig.7).

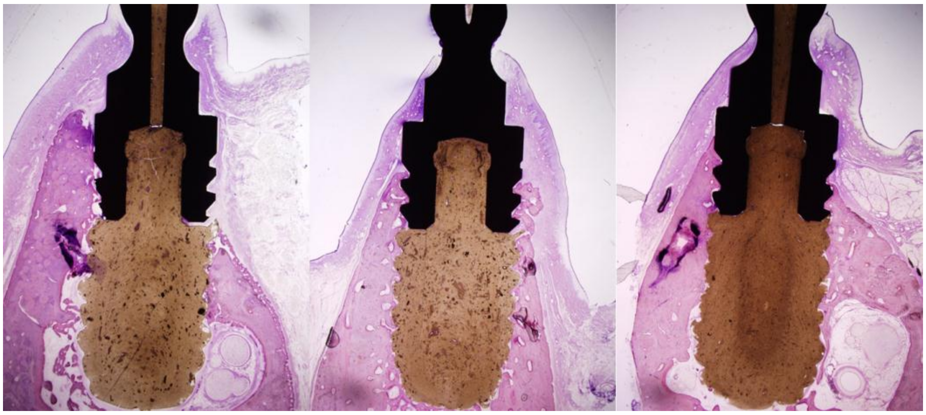

Figure 7. absorbable implant histomorphometric analysis.(original magnification 100) Left: 4 weeks, center: 8 weeks, right: 12 weeks

The images were analyzed by an ScopeEye(Tecsan, Seoul, Korea). BIC and BA were measured based on the conventional histomorphometric method [24]. For statistical analysis, ANOVA test was performed to show differences between the means of implant healing periods using SPSS 19 (SPSS Inc., Chicago, IL). Pearson' s correlation analysis was also conducted to show correlations between histomorhphometic and micro-CT analysis measurements.

# RESULTS

The reconstructed volumes of the bone and implant after segmentation are 3D rendered by healing periods (Fig. 8). We can observe increase in the implant absorption with increase of the healing period through the 3D reconstructed images. The absorption aspect of an implant at 8 weeks is quite different according to the implant thread positions in 3−dimensionally.

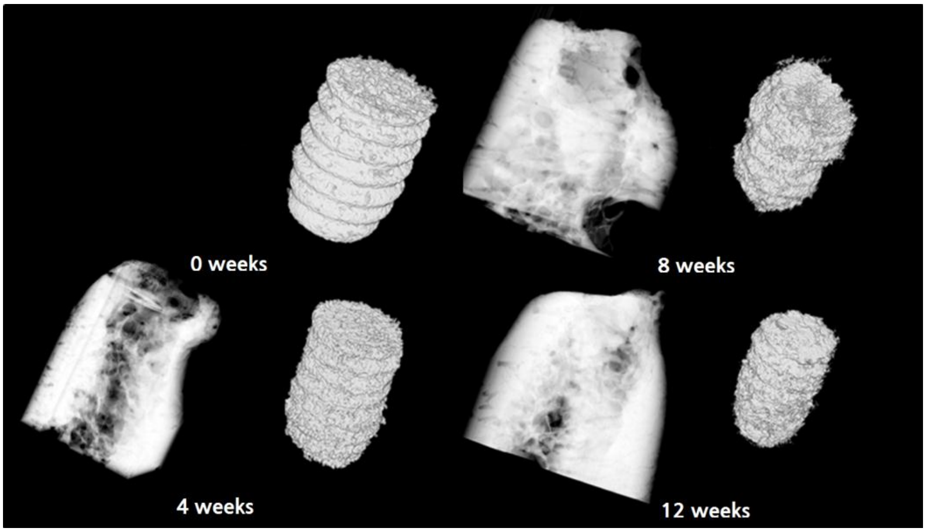


Figure 8. implant and bone volume rendering. left top: non installed implant. It was used to calculate volumetric absorption as a control.

Table 2 shows the distribution of implants used for analysis, placed in the lower jaw of beagle dogs.

**Table 2.** Distribution of implants used for analysis.

| Period | Implantation site | Number |
|---|---|---|
| 4 weeks | the 2nd premolar | 4 |
| | the 4th premolar | 4 |
| 8 weeks | the 2nd premolar | 3 |
| | the 4th premolar | 4 |
| 12 weeks | the 2nd premolar | 3 |
| | the 4th premolar | 3 |

The volumetric absorption (VA) of the implant area was 23.46±5.25% at 4 weeks, 38.89±2.46% at 8 weeks, and 41.94±4.51% at 12 weeks after implant placement. The means increased significantly with an increase in the healing period ($p<.01$ ANOVA) (Table 2). The volumetric bone−implant contact ratio (VBIC) was 17.67±3.20% at 4 weeks, 25.23±4.36% at 8 weeks, and 36.18±4.33% at 12 weeks. The means also increased significantly with an increase in the healing period ($p<.01$ ANOVA) (Fig.9, Table 3).

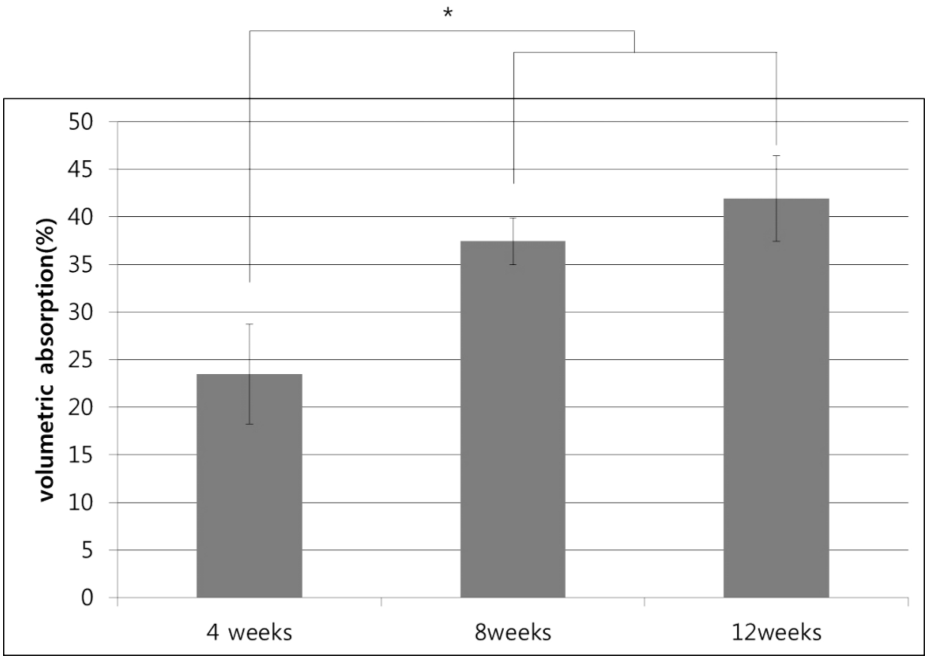

Figure 9. Mean percentages of VA(volumetric absorption). The VA men did show significant difference. (* Statistical difference between baseline and 8–12 weeks)

**Table 3.** Volumetric absorption (VA) and bone implant contact (VBIC) of absorbable implants with treatment period by micro-CT analysis (Mean±Std).

| Period | 4 weeks | 8weeks | 12weeks |
|---|---|---|---|
| VA (%) | 23.46 ± 5.25 | 38.89 ± 2.46 | 41.94 ± 4.51 |
| VBIC (%) | 17.67 ± 3.20 | 25.23 ± 4.36 | 36.18 ± 4.33 |

* Average ± standard deviation

The volumetric bone-implant contact ratio (VBIC) was 17.67±3.20% at 4 weeks, 25.23±4.36% at 8 weeks, and 36.18±4.33% at 12 weeks. The means also increased significantly with an increase in the healing period ($p<.01$ ANOVA, $p<0.05$ the turkey's multiple comparison test) (Fig.10, Table 4).

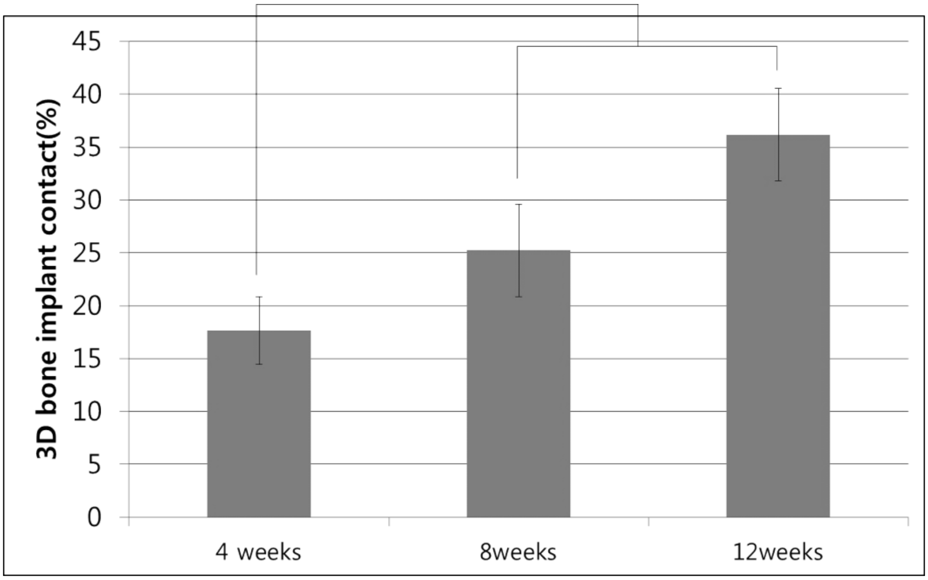

Figure 10. Mean percentages of VBIC(volumetric bone-implant contact). The VBIC mean did show significant difference. (* Statistical difference between baseline and 8-12 weeks

The BA by histomorphometric analysis was 62.07±8.43% at 4 weeks, 72.25±27.91% at 8 weeks, and 82.01±21.34% at 12 weeks after implant placement. It increased with no significant differences between periods ($p>.05$ ANOVA) (Table3). The BIC was 30.57±6.59% at 4 weeks, 32.20±9.13% at 8 weeks, and 35.50±10.63% at 12 weeks (Fig.11). They also increased with no significant differences ($p>.05$ ANOVA) (Fig.12, Table 4).

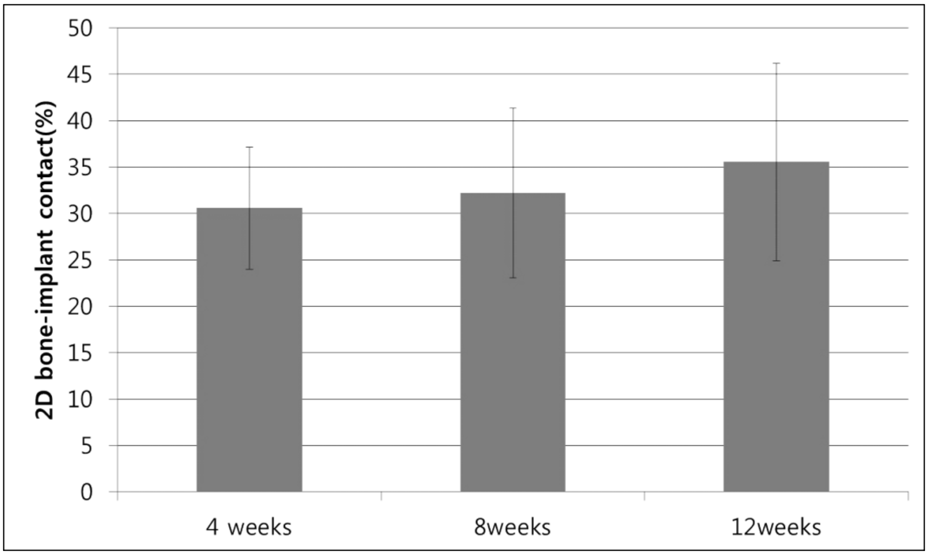


Figure 11. Mean percentages of BIC(bone−implant contact). The BIC mean did not show significant difference.

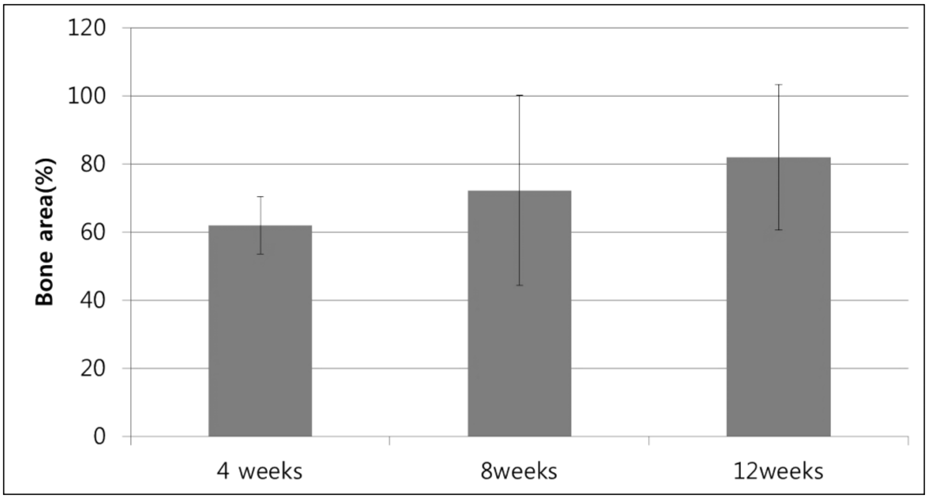


Figure 12. Mean percentages of BA(bone area). The BA mean did not show significant difference.

**Table 4.** BA and BIC of absorbable implants with treatment period by histomorphometric analysis (Mean±Std).

| 기간 | 4 weeks | 8weeks | 12weeks |
|---|---|---|---|
| BA (%) | 62.07 ± 8.43 | 72.25 ± 27.91 | 82.01 ± 21.34 |
| BIC (%) | 30.57 ± 6.59 | 32.20 ± 9.13 | 35.50 ± 10.63 |

* Average ± standard deviation

Table 5 shows Pearson's correlation coefficients between measurements by micro-CT and histomorphometric analyses. The volumetric bone-implant contact ratio (VBIC) was correlated with the volumetric absorption (VA) significantly ($p<.00$) (Fig.6) and with bone-implant contact ratio (BIC) ($p<.1$). The BIC showed a significant correlation with VA ($p<.1$). The bone area (BA) showed no correlations with other parameters.

**Table 5.** Pearson's correlation coefficients between histomorphometric and micro-CT analyses (*p <.01, **p<.1).

| | | BIC | BA | VBIC | VA |
|---|---|---|---|---|---|
| BIC | correlation | | 0.03 | 0.34 | 0.31 |
| | p-value | | 0.45 | .05** | 0.07** |
| BA | correlation | 0.03 | | 0.23 | 0.33 |
| | p-value | 0.45 | | 0.86 | 0.68 |
| VBIC | correlation | 0.34 | 0.26 | | 0.46* |
| | p-value | 0.05** | 0.87 | | 0.00 |
| VA | correlation | 0.31 | 0.33 | 0.46* | |
| | p-value | 0.07** | 0.68 | 0.00 | |

# DISCUSSIONS

Surgical technique, quality and quantity of bone, and dental health conditions are important factors for successful implant treatment. Especially osseointegration is known [1] to be affected by factors such as surficial characteristics of the implant and biological compatibility.

Various researches have been conducted to increase osseointegration of the implant. According to studies [25, 26], such as of Piattelli' s (1991), the roughness increase on the surface of the implant tends to cause the increase of BIC. Recently, studies related to SLA (acid etching) method, which uses corrosion of the surface in order to increase osseointegration, have been widely spread [27. 28].

Compared with researches for successful implant treatment by increasing osseointegration, there was relatively less interest in adaptive change of the jaw bone during childhood and adolescence. By the social norm, the proper installation period of any implants is determined to when the maturing process is over. Existing implant installation on younger patients who are still at their growing phases, growth of alveolar or jaw may cause lower sedimentation [2].

Bone graft is needed for future implant installation by loss of alveolar in any external damage, congenital teeth loss, and accidental loss of teeth during the growing phase cases. Hence, there is a need to develop the implant that can be installed for childhood and adolescence patient.

The absorbable implant is being developed to minimize the side effect of lower sedimentation by used of existing non absorbable implant for young patients. The absorbable implant is expected to be absorbed internally even during the cases of lower sedimentation after the installation. The main material of the absorbable implant is TCP (tricalcium phosphate), and it is proved to form new bone tissue around the damaged BA along with its absorbability. It can also prevent drastic reduction of strength by conjunction with bioabsorbable ceramics PLA [29] which is used for orthopedics implant material.

Measurement of osseointegration is one of the essential elements for estimating success rate of implant treatment. Analyzing BIC and BA through the histomorphometric method is one of the ways to measure osseointegration. The histomorphometric analysis has its advantage in high resolution and contrast. On the contrary, it has disadvantages of complex procedure for creating slides and of providing only 2D analysis.

The micro-CT based analysis method showed high correlation with the histomorphometric method [21]. Ko (2010) proposed a new method [30] for quantification of osseointegration by using the micro-CT. It is different from already existing methods as it measures BCA (Bone Contact Area) and BCAR (Bone Contact Area Ratio) to measure osseointegration by using the micro-CT.

Compared to the results from osseointegration analysis between the histomorphometric method and the micro-CT method that showed significant correlation for existing titanium implants, the significant correlation between the two methods for the absorbable implant were not found. The lack of correlation might be caused by the certain limitations that the histomorphometric analysis has for measuring BIC and BA.

Position of the implant thread and its radius setting are limited by its absorption status over time, and it is also likely to reflect the subjectivity of the experimenter. Therefore, analysis of osseointegration by the histomorphometric method did not show statistically significant difference.

Ultimately, in condition where the thread of the imaplant is changing over time of its installation, unlike the past implants, measurement of BA and BIC from existing histomorphometric analysis is inefficient to provide significant information for osseointegration evaluation.

In the other hand, VA showed correlation with BIC and tendency to increase over time. Thus, VA based on the micro-CT method can be proposed as a new quantitative parameter for oesseointegration for the absorbable implant.

The method of segmenting each BA and implant area for the micro-CT analysis from this study also can be helpful for quantifying the VA of implant with bio absorbable ceramics material in orthopedics.

If change in implant area is examined by using existing histomorphometric analysis to quantify the absorption rate, there is limitation that it only provides 2D analyses. Total absorption cannot be measured only by slides fraction. Bone areas, from osseointegration measurement by using the histomorphometric analysis, were consecutively as following: 4 weeks 62.07 8.43%, 8 weeks 72.25 27.91%, 12 weeks 82.01 21.34%.

The BIC rate was consecutively as following: 4 weeks 30.5

6.59%, 8 weeks 32.30 9.13%, and 12 weeks 35.55 10.63% and it did increase based on the duration, but statistical significance was not verified (Fig. 11, 12).

Generally, two structures of the bone and implant were separated by using a threshold method in micro-CT analysis [31, 32]. The adequate thresholds for the bone and the implant were selected by superimposing segmented images over original gray scale images [30]. Since the absorbable implant consisted of composite materials, it has intrinsically inhomogeneity of pixel intensity in micro-CT images other than titanium implants. So, it is not possible to apply the threshold method directly, which is an algorithm based on the homogeneity of image intensity. We applied the area-based confidence connected segmentation method which is based on an region growing algorithm. The method segmented the bone and the implant by taking a seed region as an initial segmentation and then iteratively adding all connected voxels that had voxel intensity within a dynamically defined range [22].

VBIC and VA was measured by the micro-CT method with its 3D analysis ability. They did show significant different BIC in 4 weeks 17.67 3.20%, 8 weeks 25.23 4.36%, and 12 weeks

36.18 4.33%; VA in 4 weeks 23.46 5.25%, 8 weeks 38.89 2.46%, and 12 weeks 41.94 4.51% ($P < 0.05$). Also, micro-CT analysis showed significant correlation ($r=0.439$, $p<0.01$) between the VBIC and VA (Fig. 9, 10).

When evaluating implants with titanium material, As past experiments considered bio-absorbable characteristic of the absorbable implant, it appears that there is a need for altered process for osseointegration evaluation. BA and BIC between the absorbed implant and the bone are affected by the duration and the speed of absorption. Hence, it was expected the absorption based on duration, to play an important role when evaluating the osseointegraion of absorbable implant.

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# 국문 초록


**서론:** 본 연구의 목적은 micro-CT 분석 결과를 통해 골 융합도 평가의 요소로 체적 흡수율을 정량화 하는데 있다. 우리는 micro-CT 영상을 이용하여 흡수성 임플란트 소재에 대한 새로운 방법의 골융합도 평가방법을 개발하였고 조직형태계측 분석간의 상관관계를 측정하였다.

**방법:** 우리는 웅성견 실험동물 7 마리에 대해 하악 제 2, 4 소구치를 발치하여 약 3 개월간의 치유기간을 거친 후 PLA-TCP 30%(polylactic acid-tricalcium phosphate)가 처리된 흡수성 임플란트를 좌, 우 각 2 개씩 식립하였다.

식립 후 시술 4 주, 8 주, 12 주가 경과 실험동물에 대해 임플란트가 포함되도록 조직을 절제해 micro-CT 촬영을 하였고 전체 28 개의 임플란트 가운데 파손된 7 개의 임플란트를 제외한 21 개의 샘플에 대한 분석을 실시하였다.

Micro-CT 촬영 결과로부터 임플란트의 흡수율과 골-임플란트 접촉율(BIC) 측정을 위해 confidence connected segmentation, connected threshold segmentation, 모폴로지 연산 및 레이블링의 영상처리 과정을 수행하였고 3 차원적 분석을 하였다.

또한, 조직형태계측 분석방법을 통한 2 차원적 분석을 위해 절제된 조직의 중심부위를 협설측 방향으로 절제하여 조직 슬라이드 시편을 제작하였고 골-임플란트 접촉율 및 골 면적율을 측정하였다.

**결과:** Micro-CT 분석 기반의 체적 흡수율(VA) 및 체적 골-임플란트 접촉율(VBIC) 측정 결과, 두 결과 모두 회복 기간에 따라 증가하였고 통계적으로 유의한 차이(P < 0.05)를 보였다. 골 면적율과 골-임플란트 접촉율 측정결과, 식립 기간에 따라 수치가 증가하였지만 통계적인 유의성을 검증할 수 없었다.

유의한 통계적 결과를 보인 Micro-CT 분석 기반의 체적 흡수율과 골-임플란트 접촉율 결과 간 상관관계를 분석한 결과 상관계수 0.463 에서 유의한 상관성(P < 0.01)을 보였다.

**결론:** 두 분석 방법의 결과를 종합해 볼 때 기존의 조직형태계측 분석 방법은 기간에 따라 변형이 이뤄지는 흡수성 임플란트를 분석하는데 한계를 보였다. 반면, micro-CT 분석방법을 통한 3 차원적 분석방법은 체적 흡수율 및 골-임플란트 접촉율을 측정하는데 상대적으로 유리하였고 유의한 결과를 보였다.

흡수성 임플란트의 체적 흡수율은 골-임플란트 접촉율과 상관성을 보이며 흡수성 임플란트의 골융합도 평가를 위한 새로운 파라미터 정보를 제공하였다. 따라서 흡수성 임플란트의 골융합도 평가를 위해서는 기존의 임플란트 골융합도 평가 방식과 다르게 체적 흡수율 정량화가 필요함을 예측할 수 있다.

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**주요어 : 흡수성 임플란트, 임플란트 흡수율, 골 임플란트 접촉율, 골 면적율, 조직형태계측 분석, micro-CT**

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