

# Osseointegration of hydroxyapatite-coated implants with new bone in one stage sinus floor elevation without bone substitute - A long-term animal experiment using canine frontal sinuses -

Cintia Yuki Fukuoka <sup>1)</sup>, Takao Watanabe <sup>2)</sup>, Masato Matsuo <sup>2)</sup>,  
Akira Iimura <sup>2)</sup> and Toshimitsu Okudera <sup>2)</sup>

## Abstract

The aim of this study is to histologically compare the osseointegration of 2 types of hydroxyapatite (HA)-coated implants, a JHA implant (Kyocera Medical Ltd, Japan) and a KHA implant (Zimmer Ltd, USA), with the new bone forming in the space under the lifted membrane (SULM) in a long-term animal experiment of one stage sinus floor elevation (SFE), without bone substitutes and mechanical loading, using canine frontal sinuses. Sixteen implants, 8 JHA and 8 KHA were placed in 4 postmenopausal beagles for 3 and 6 months. Histological observations and histomorphometric measurements were carried out with light-microscopy using hematoxylin and eosin stained undecalcified specimens. Statistical significant differences were evaluated by one-way ANOVA.

The new bone formation was observed on a large area of the sinus wall and the implant surface in the SULM at 3 and 6 months in both groups. Bone implant contact rate with new bone in the SULM was  $88.8 \pm 10.5\%$  at 3 months and  $77.0 \pm 7.9\%$  at 6 months in JHA group, and  $85.3 \pm 7.6$  and  $87.3 \pm 17.9\%$  in KHA group, respectively. There was no statistical significant difference between the groups. It was concluded that both types of HA-coated implants have similar properties to promote a superior osseointegration with the new bone forming in the SULM. Furthermore, the new bone which osseointegrated with the HA-coated implants has a possibility to remain for a long time.

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## 1. Introduction

SFE was first performed for implant patients by Tatum in 1975 and first published by Boyne in 1980<sup>1)</sup>. The outline of the original SFE by Tatum<sup>2)</sup> was one stage, lateral approach, titanium

implants and autologous bone grafting. In his SFE procedures, a part of the placed implant was positioned in the space under the lifted membrane (SULM). When the surgery finished, the SULM was filled by blood cells, but new bone was not yet present around the placed implant. Our animal experiments of one stage SFE without bone

1) Department of Biomaterials and Oral Biology, Sao Paulo University School of Dentistry, Brazil

2) Department of Oral Science, Graduate School of Dentistry, Kanagawa Dental University, Kanagawa, Japan

substitutes<sup>3)</sup> showed granulation tissue within a few days and then new bone started to form from the sinus wall a week later. At 2 months, the new bone volume reached its peak and then decreased. At 6 months, a small amount of new bone remained on the sinus wall. However, osseointegration between the machine-polished titanium implants and the new bone in the SULM was not seen<sup>4)</sup>. The bone implant contact rate (BIC) was 2% at most. Generally, HA-coated implants show superior osseointegration with pre-existing bone than the machine-polished titanium implants<sup>5)</sup>. The aim of this study is to histologically compare the osseointegration of 2 types of HA-coated implants, a JHA implant (Kyocera Medical Ltd, Japan) and a KHA implant (Zimmer Ltd, USA), with the newly formed bone in the SULM in an experiment of one stage SFE without bone substitutes, using canine frontal sinuses.

## 2. Materials and Methods

### 1) Animals:

After a period of acclimation 4 postmenopausal female beagle dogs with a mean body weight of 10.3kg were used. They were raised at a laboratory providing animal management facilities and fed standard commercial dry canine food and water *ad libitum*.

### 2) Implants:

A total of 16 HA-coated implants, 8 JHA implants, 55% crystalline HA-coated tapered implants (POIEX, FINATITE, 3.7mm in width and 8mm in length, Kyocera Medical Ltd, Japan) and 8 KHA implants, 95% crystalline HA-coated implants (SPLINE TWIST, 3.75mm in width and 8 mm in length, Zimmer Ltd, USA) were placed in canine frontal sinuses (Fig.1).

### 3) Surgical procedures:

An intramuscular injection of medetomidine

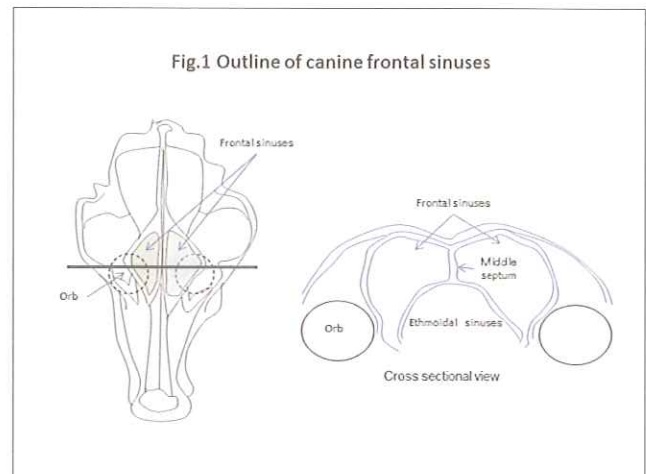


Fig. 1: Outline of canine head and frontal sinuses

hydrochloride (Domitor, Orion Pharma Inc., Finland) 0.05ml/kg followed by intravenous anesthesia with 0.5ml/kg of sodium pentobarbital (Nembutal, Dainippon Medical Pharma Ltd, Japan) were performed. Local anesthesia was applied to the skin with 2% lidocaine hydrochloride (Xylocain, Fujisawa Medical Corp, Japan).

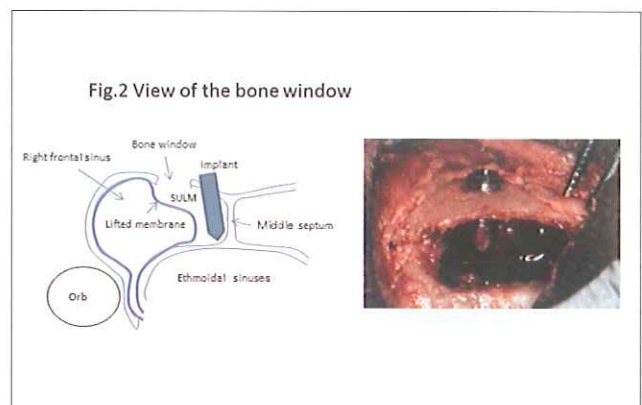


Fig. 2: View of the bone window, Blood clot and two third of the placed implant can be seen at the space under the lifted sinus membrane.

In the first surgery, a 3mm full thickness incision was made in the middle of the canine forehead. The skin flap with the periosteum was detached and a rectangular area of 10mm in length and 8 mm in width was made with a 2mm groove (Fig.2). The rectangular bone fragment was removed to open a bone window in the forehead. The sinus



membrane was detached from the sinus wall and lifted through the bone window. Two holes, 3.5 mm in diameter and 1.1mm in depth, were made beside the bone window using a cylindrical rotary instrument. The rotation was stopped right after bone penetration. One JHA and one KHA implant were placed along the middle septum with 5Ncm of torque, in each sinus. Finally, the skin flap with the periosteum was repositioned and sutured.

Three months later, the second implant surgery was performed in the right frontal sinus, following the same procedure. Three months after the second surgery, sacrifice was carried out by intramuscular injection using medetomidine hydrochloride (Domitor, Orion Pharma Inc, Finland) 0.05ml/kg and an overdose infusion of sodium pentobarbital.

#### 4) Periotest analysis:

Soon after sacrifice, the skin tissue with the periosteum was removed and then the platform of the placed implant was exposed. An adapter was set into the placed implant at the forehead. The mobility of implants was checked using Periotest (Medizintechnik Gulden Ltd. Germany).

#### 5) Histological observation (Fig.3):

Bone blocks, 8mm×25mm×25mm in size, from the left and right frontal sinuses were removed and placed in 10% neutral formalin for two weeks. Afterwards, they were cut in two at the center site, dehydrated and embedded in VLC resin (MG3000, Exact Ltd, Germany). The blocks comprising the implants were cut into small 2 mm×20mm×20mm pieces. They were adhered to an acrylic plate (TECHNOVIT7200, Exact Ltd, Germany) and sliced using a cut machine (MG4000, Exact Ltd, Germany), so that the center of the implant appeared on the specimen's surface. Then hematoxylin and eosin staining was carried out. The histological observation was performed using an E800 light microscope (Japan Optical Co, Ltd, Japan).

#### 6) Histomorphometric measurement:

At the sinus wall (pre-existing bone):

- (1) Sinus wall thickness; SWTw(mm)
- (2) Bone implant contact rate with pre-existing bone in the sinus wall; BICw(%)

In the SULM:

- (3) New bone height from sinus wall to the top of new bone surrounding the implant; NBHs(mm)
- (4) Rate of new bone surrounding the implant surface; RNBs(%)
- (5) Bone implant contact rate with new bone; BICs(%)

#### 7) Statistical Analysis:

Data groups were statistically compared using variance analysis, with multiple comparison of Tukey. The level of significance was set at  $p < 0.05$  and  $P < 0.01$ . Group means and standard deviation were presented.

This experiment was approved and performed in strict accordance with the Animal Care Committee guidelines of Kanagawa Dental University (No.259).

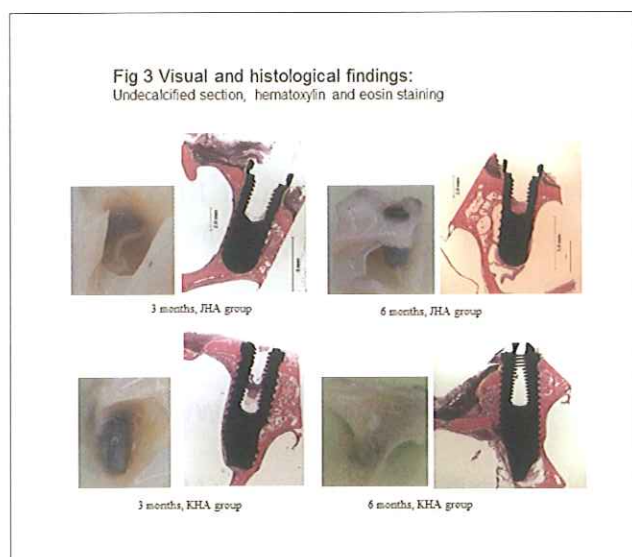


Fig. 3: V Visual and histological findings of, hematoxylin and eosin staining on Undecalcified section

### 3. Results

#### 1) Visual findings of the placed implant in the SULM (Fig.3)

A small amount of the SULM remained on the sinus wall and on the placed implant surface at 3 and 6 months after surgery in both groups. The implant, which was covered by a thin layer of whitish soft tissue, protruded from the sinus wall. No blood clot was seen.

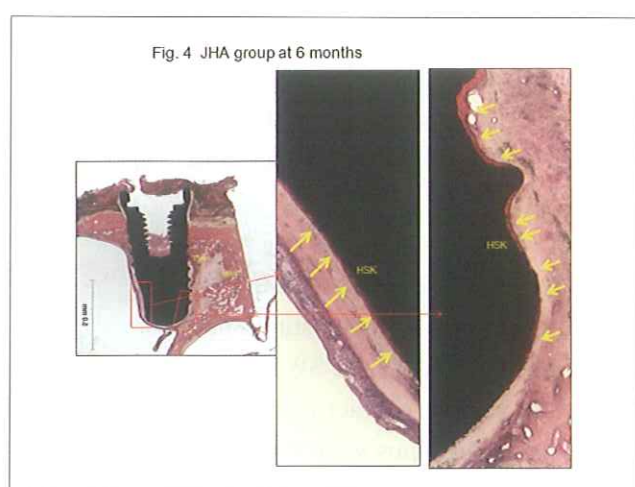


Fig. 4: JHA group at 6 months.  
The arrows indicate a thin layer of remaining new bone (HSK) osseointegrated with the implant surface.

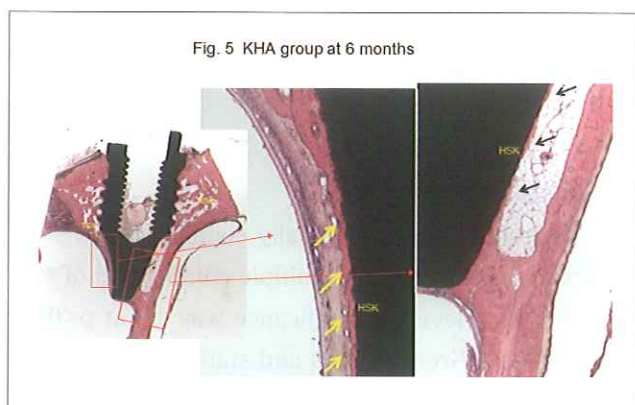


Fig.5: KHA group at 6 months  
TSN at the implant base and NBW on the sinus wall were observed. The arrows indicate HSK osseointegrated with the implant surface. KHA group showed similar histological findings, at 3 and 6 months, to JHA group.

#### 2) Histological findings, undecalcified specimens with hematoxylin and eosin staining (Fig.4, 5)

The SULM was composed of new bone and fibrous connective tissue remaining in the space between the placed implant and the sinus wall at 3 and 6 months in both groups. Under low magnification, tent-shaped new bone remaining around the base of the placed implant (TSN) and a small volume of new bone on the sinus wall at the site far from the placed implant (NBW) were observed at 3 and 6 months in both groups. They were not seen in the spaces center and under the lifted membrane. Most new bone observed in this study consisted of matured trabecular bone with lamellar structure and resorption pits. It showed static matured bone where development was already completed. Under high magnification, a thin layer of new bone (HSK), roughly 50~100 $\mu$ m thick was observed on the placed implant surface. HSK was also seen on the lumen side surface of the implant as well as on the wall side and continued to be visible 6months after surgery in both groups. There were no significant differences in the histological findings between the JHA and KHA groups.

#### 3) Periotest analysis

Periotest analysis in JHA group revealed that the mean value increased from  $1.5 \pm 0.7$  at 3months to  $3.6 \pm 2.1$  at 6 months ( $P < 0.05$ ). The KHA group showed a value of  $0.4 \pm 1.8$  at 3 months and  $-1.0 \pm 1.1$  at

Table 1 : PERIOTEST analysis (Periotest value)

1) Sinus wall thickness: SWTW		
(mm)		
Group	3M	6M
JHA	$1.1 \pm 0.2$	$1.2 \pm 0.2$
KHA	$1.1 \pm 0.2$	$1.2 \pm 0.3$
(n=4)		



6 months. KHA group, at 6 months, had statistically significant lower Periotest values in comparison to the JHA group ( $P<0.01$ ). However, Periotest values in both groups were less than 10, indicating a good clinical osseointegration.

#### 4) Histomorphometric measurement

##### (1) Sinus wall thickness (Table 1); SWTw(mm)

SWTw in JHA group was  $1.1\pm0.2$ mm at 3 months, and  $1.2\pm0.2$ mm at 6 months. While in the KHA group, it was  $1.1\pm0.2$ mm at 3 months and  $1.2\pm0.3$ mm at 6 months. Both groups showed similar results and the average SWTW was 1.1mm in all groups. There were no statistical difference between them.

Table 2 : Sinus wall thickness; SWTW (mm)

2) Bone implant contact rate in sinus wall (pre-existing bone); BICw (%)			
Group	3M	6M	(%)
JHA	$40.4\pm33.4$	$32.4\pm29.1$	
KHA	$51.9\pm44.6$	$65.2\pm18.9$	
(n=4)			

##### (2) Bone implant contact rate with pre-existing

bone in the sinus wall (Table 2); BICw(%)

After 6 months, BICw ranged from  $32.4\pm29.1\%$  in JHA group to  $65.2\pm18.9\%$  in KHA group.

There were no statistical difference between the groups.

Table 3 : Bone implant contact rate with pre-existing bone in the sinus wall; BICw (%)

3) New bone height in SULM: NBHs (mm)			
Group	3M	6M	(mm)
JHA	$5.8\pm2.9$	$8.8\pm2.7$	
KHA	$5.8\pm2.2$	$6.3\pm2.1$	
(n=4)			

##### (3) New bone height in the SULM (Table 3); NBHs(mm)

NBHs ranged from  $5.8\pm2.2$ mm at 3 months in KHA group to  $8.8\pm2.7$ mm at 6 months in JHA group. There were no statistical NBHs differences between 3 and 6 months in both groups.

Table 4 : New bone height in the SULM; NBHs (mm)

4) Rate of new bone covering the implant surface in SULM: RNBs (%)			
Group	3M	6M	(%)
JHA	$70.6\pm21.4$	$75.6\pm16.2$	
KHA	$65.3\pm4.9$	$78.6\pm11.3$	
(n=4)			

##### (4) Rate of new bone surrounding the implant

surface in the SULM (Table 4); RNBs(%)

RNBs increased from  $65.3\pm4.9\%$  at 3 months to  $78.6\pm11.3\%$  at 6 months in KHA group ( $P<0.05$ ). There were no statistical RNBs differences between both groups.

Table 5 : Rate of new bone surrounding the implant surface in the SULM; RNBs(%)

5) Bone implant contact rate with new bone in SULM: BICs (%)			
Group	3M	6M	(%)
JHA	$88.8\pm10.5$	$77.0\pm7.9$	
KHA	$85.3\pm7.6$	$87.3\pm17.0$	
(n=4)			

##### (5) Bone implant contact rate with new bone in the SULM (Table 5); BICs(%)

The BICs in the JHA group was  $88.8\pm10.5\%$  at 3 months, and  $77.0\pm7.9\%$  after 6 months. The KHA group BICs at 3 and 6 months were  $85.3\pm7.6$  and  $87.3\pm17.0\%$ , respectively. Both

groups showed higher BICs than BICw at 3 and 6 months. There were no statistical BIC differences between 3 and 6 months, in both groups.

#### 4. Discussion

The canine frontal sinus membrane has a ciliated columnar epithelium which is histologically similar to the human maxillary sinus. The majority of implant patients are postmenopausal women, ranging from 50 to 60 years<sup>6)</sup>. For this reason, postmenopausal dogs were used in this study. Canine frontal sinus wall has a thin cortical bone, ranging from 1.1 to 1.2mm in width (Table 1). Most areas of the placed implants were exposed inside the SULM (Fig.2). Various types of bone substitutes, like synthetic HA,  $\beta$ -TCP ( $\beta$ -tricalcium phosphate), sintered bovine bone granules with human growth factors, PRP and BMP have been reported to fill the SULM, to improve the new bone formation and to promote osteoconduction and osteoinduction<sup>7-14)</sup>. In this study, no bone substitutes were used. The relationship between bone substitutes and osseointegration with the newly formed bone in the SULM should be investigated.

Concerning new bone formation in the SULM, in one stage SFE without grafting, Lai reported  $2.26 \pm 0.92$ mm and  $2.66 \pm 0.87$ mm at 3 and 9 months follow-up<sup>15)</sup>. Thor showed 6.51mm using ITI-SLA after 1 year<sup>16)</sup>. Chen observed 4.5mm, ranging from 3 to 8mm, in 47 Astra Tech implants after 2 years follow-up<sup>17)</sup>. We found 4mm in height of new bone in a clinical case using a rough surface titanium implant 3 years later<sup>18)</sup> and Nedir reported  $3.0 \pm 1.4$ mm at the implant sites using ITI-SLA after 10 years<sup>19)</sup>. This study showed sufficient NBHs, ranging from  $5.8 \pm 2.2$ mm at 3 months in the KHA group to,  $8.8 \pm 2.7$ mm at 6 months in the JHA group. The implant placed in an one stage SFE can develop sufficient new bone and remain in the SULM over a long time, even if bone

substitutes are not used.

The new bone observed at 3 and 6 months in this study, consisted of matured trabecular bone with lamellar structure and resorption pits. It was considered to be a static bone, during the remodeling phase, where its development was already finished. NBW on the sinus wall and TSN at the implant base were observed at all stages, in both groups. Under high magnification, HSK covered a wide area of the placed implant surface in the SULM. Both groups showed similar histological findings at 3 and 6 months.

Ribin explained that the innate osteogenic potential of the Schneiderian membrane may be the main reason for successful formation of bone with one stage SFE, without bone substitutes<sup>20,21)</sup>. However, new bone formation from the membrane was not observed in this study. It was in fact, fibrous connective tissue. The new bone formation in the SULM might be a reactive bone regeneration caused by surgical stimulation, such as lifting the sinus membrane and implant placement, that stimulated precursor cells in the periosteum and endosteum of the sinus wall. It does not depend on the type of grafting material used.

The original definition of osseointegration is a direct structural and functional connection between ordered living bone and the surface of a load-carrying implant<sup>22)</sup>. In the term, there is a recognition that nonvital components are reliably and predictably incorporated into living bone, and that incorporation between them can persist under all normal conditions of loading<sup>23)</sup>. It is used when there is no progressive relative movement between the implant and the bone with which it has direct contact<sup>24)</sup>. Periotest analysis in this study revealed that both groups were less than 10, indicating good clinical osseointegration. BIC by histological analysis is frequently used as a parameter for evaluating osseointegration<sup>25-27)</sup>. In canine experiments, a BIC of 60 to 67% from 4 to 8 weeks<sup>28)</sup>, 60 to 67% from 4 to 26 weeks<sup>29)</sup>, and 30 to 60% at 11 to 12 months were



reported<sup>30)</sup>. In rabbit experiments, a ratio of 34% to 52% from 8 to 24 weeks was observed<sup>31)</sup>. Hurzeler showed higher BIC for titanium implants with rough surface in comparison to implants with machine-polished surface, 45.8 and 35.9%, respectively. BIC in osteotome sinus floor elevation (OSFE) without grafting (40.05%) was higher than those with  $\beta$ -TCP grafting (23.30%) at 24 weeks, using an animal experiment, in a report by SI<sup>32)</sup>. He concluded that spontaneous new bone formation and better bone-to-implant contact were found for OSFE without grafting, using titanium implants with rough surface. However, our previous animal experiment showed that osseointegration of machine-polished titanium implants with the new bone in the SULM was not observed<sup>3)</sup>. The BIC was 2% at most.

Implants with HA coating were reported as achieving a high BIC of 46%<sup>33)</sup> to 99%<sup>34)</sup> in sinus augmentation immediately followed by implant surgery. The HA-coated implants can promote an elution of calcium ions and phosphate to favor the osteoconductivity by the higher crystallization rate of HA. KHA implants have 95% crystalline HA coating on the surface. JHA implants have 55% crystalline HA coating with about 20 $\mu$ m thickness, while KHA implants have HA coating with 50 to 70 $\mu$ m. During implant placement, in order to avoid the destruction of the HA coating when the implant causes friction with the surrounding bone, the KHA implants have a cylinder shape with the same diameter from the neck to the apex of the implant. On the other side, JHA implants have an enhanced adhesion between HA coating and the titanium surface that minimizes stress fractures. JHA implants are screw-shaped with the maximum diameter at the neck part, to promote primary fixation. This study found the BIC of both KHA and JHA implants achieved sufficient osseointegration, with more than 80% of BIC, and no differences in the histological findings and histomorphometric measurements. Periotest values also indicated sufficient clinical osseointegration. There was no

difference between osseointegration with the new bone at 3 and 6 months in both groups. However, it was significantly higher than the osseointegration reported by Hidaka<sup>4)</sup> using machine-polished implants. This study showed that both HA-coated implant groups have superior surface properties for osseointegration with the newly formed bone in the SULM. It is considered that osseointegration between the new bone and HA-coated implants can remain for a long time, at least 6 months in an one stage SFE, even if bone substitutes are not used. Generally, two stage SFE is used for cases when the available bone volume between the sinus floor and the alveolar bone crest is below 5mm<sup>35)</sup>. In a two-stage SFE, the new bone forms first in the SULM. The new bone is used as a pre-existing bone to place an implant in the second stage surgery. Consequently, the mechanism of osseointegration with new bone in a two-stage SFE can be understood as osseointegration with the pre-existing bone as reported by the Bränemark concept<sup>22)</sup>. Meanwhile, the mechanism of osseointegration with the new bone in the SULM in one stage SFE is unclear. In the next study, rough surface titanium implants will be used to compare the results using HA-coated implants.

## 5. Conclusion

It was concluded that both types of HA-coated implants have similar properties to promote a superior osseointegration with the new bone forming in the SULM. Furthermore, the new bone which osseointegrated with HA-coated implants has the possibility to remain for a long time.

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