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Application of Octacalcium Phosphate and Collagen Composite for Bone Augmentation with Sinus Floor Elevation in Humans

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Abstract

Octacalcium Phosphate (OCP) and collagen composite (OCP/Col) was recognized as a highly osteoconductive bone substitute material based on *in vitro* and *in vivo* studies. In this study, OCP/Col was applied for bone augmentation with sinus floor elevation as a clinical trial. This study evaluated the progress of bone formation via OCP/Col and dental implant treatment. OCP/Col was applied in 3 patients, and these patients were evaluated subsequent bone formation radio graphically and examined the newly formed bone histological and via Fourier transform infrared spectroscopy. Radio graphical examination showed that OCP/Col converted to hard tissue with radiopacity within 6 months of implantation. Histological examination confirmed normal bone tissue in a specimen and FTIR revealed characteristics of bone-like apatite. There was no problem after the treatment of the dental implant. This study suggested that OCP/Col could be a bone substitute material for bone augmentation procedures involving sinus floor elevation.

Keywords: Bone substitute material; Bone augmentation; Dental implant treatment

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Introduction

Various materials have been used as bone substitutes in cases requiring bone reconstruction [1-4]. Autologous bone grafting is the most desirable approach for bone defect reconstruction, due to its high osteoconductivity [5]. It has certain disadvantages however, including limited availability, and the morbidity associated with harvesting bone from a secondary operative site [6-8]. Calcium phosphate is used in clinical settings as a bone substitute material [1,9-11]. Some calcium phosphate products have also been used clinically as bone substitutes in dental implant surgery requiring bone augmentation [3,12-15].

Synthetic Octacalcium Phosphate (OCP) has become recognized as a highly osteoconductive bone substitute material based on *in vitro* and *in vivo* studies [16-18]. OCP has higher solubility than Hydroxapatite (HA) and beta tricalcium phosphate and is therefore more resorbable than both of those materials *in vivo* [19]. It has been reported that OCP combined with collagen (OCP/Col) facilitates bone regeneration more effectively than OCP alone [20,21], and the osteoconductivity of OCP/Col has been demonstrated in critical-sized bone defects in dogs [22-25]. Previous studies have demonstrated the effects of OCP/Col on bone regeneration small bone defects in humans, and confirmed healing at the sites of the defects [26-28]. However, to date bone augmentation using OCP/Col at sites of bone atrophy has not been investigated. There is a report of the clinical use of OCP granules to fill the space created during sinus floor elevation, but the success of the dental implant treatment was not described in that report [29]. The present study was designed to investigate whether OCP/Col could be used as a bone substitute material in bone augmentation for dental implant treatment. The current study reported the first application of OCP/Col for bone augmentation with sinus floor elevation in patients with atrophic maxilla, and evaluated their progress until the final prostheses were fitted. Furthermore, the newly formed bone was analyzed via

Figure 1: Photograph of OCP/Col discs, which are 9 mm in diameter and 1.5 mm thick. The weight percentage of OCP granules in OCP/Col was 77%. OCP/Col has almost 92% porosity and bimodal peaks of 48 μm (main pores) and 0.3 μm (minor pores), and its specific surface area (SSA) was 17.8 m^2/g.

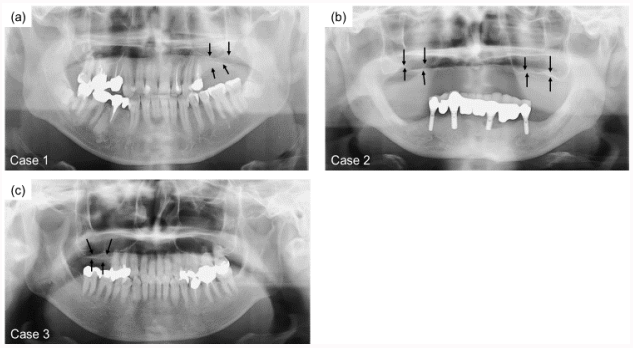

Figure 2: X-ray images of maxillary atrophic patients. (a) Case 1, the right maxilla. (b) Case 2, bilateral maxilla. (c) Case 3, the left maxilla. Arrows show the height of the alveolar crest relative to the sinus floor. The thickness of bone from the alveolar crest to the sinus floor in each case was 1 mm to 5 mm. Bone augmentation was necessary for dental implant treatment.

histological and *via* Fourier Transform Infrared Spectroscopy (FTIR) for the first time in humans.

Materials and Methods

Preparation of OCP/Col

OCP was prepared by mixing calcium acetate hydrate solution and sodium phosphate monobasic solution as described previously [16]. The precipitates were washed several times with filter-sterilized water, and then lyophilized. Sieved OCP granules (particle sizes 300 μm to 500 μm) obtained from the dried OCP were sterilized via heating at 120°C for 2hr. A previous study showed that such heating does not affect physical properties such as the crystalline structure or specific surface area of OCP granules, although increasing the temperature above 100°C induced collapse of the OCP structure due to dehydration [30]. Powder X-ray Diffraction (XRD) patterns of the processed OCP were recorded via step-scanning at 0.05-degree intervals from 3 to 60 degrees, with Cu Kα X-rays on a diffract meter (Mini Flex; Rigaku Electrical Co, Tokyo, Japan) at 30 kV and 15 mA. The range of 2θ included the primary peak (100) reflection of OCP, which was approximately 4.7 degrees. Collagen was prepared from NMP collagen PS (Nippon Meat Packers, Tsukuba, Ibaraki, Japan) and a lyophilized powder was prepared from pepsin-digested atelocollagen isolated from porcine dermis. NMP collagen PS was dissolved in filter-sterilized water and adjusted to a final concentration of 3% and pH 7.4 OCP/Col was prepared from NMP collagen PS and OCP granules. OCP was added to the concentrated collagen and mixed. The weight percentage of OCP in OCP/Col was 77%. This OCP/Col mixture was then lyophilized and discs were moulded (9-mm diameter, 1.5-mm thickness) (Figure 1). The molded OCP/Col was dehydrothermally treated (150°C, 24 hr) in a DP32 Vacuum Drying

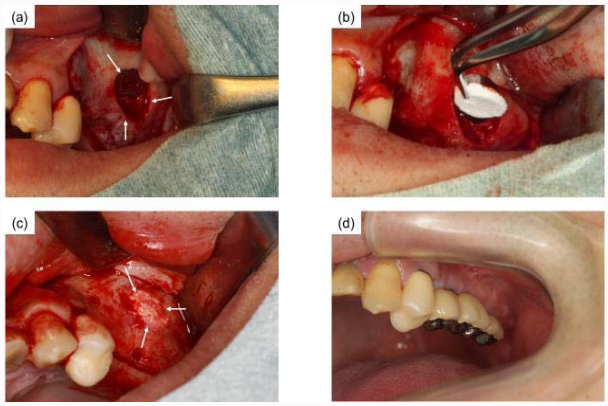

Figure 3: Photographs of sinus floor elevation in case 1 (a) Gingiva and periosteums were ablated and an oval-shaped groove was formed in the lateral wall of the maxillary sinus. A space was created from the lateral sinus wall region (arrows). (b) There was no perforation of the sinus membrane. OCP/Col discs were implanted into the space. (c) Hard tissue was confirmed at the lateral sinus wall region at 6-months after OCP/Col implantation (arrows). There were no abnormalities or any inflammation at the time of the second dental implant surgery. (d) The final prosthesis was set.

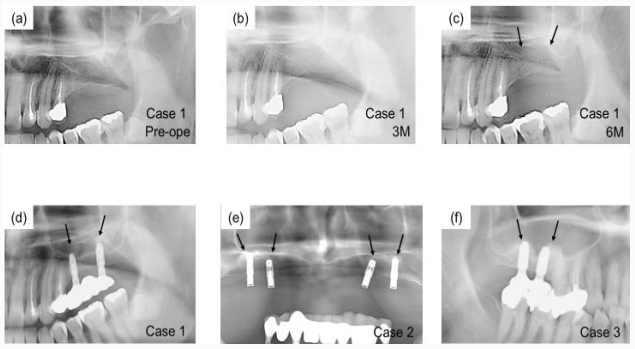

Figure 4: X-ray images after OCP/Col implantation. (a) Immediately after OCP/Col implantation in case 1. There was little radiopacity in the OCP/Col implantation region. (b) Three months after dental implant placement in case 1. The sinus floor had become unclear. (c) Six months after dental implant placement in case 1. Sinus floor augmentation was observed. (d) Twelve months after dental implant placement in case 1 (e) Twelve months after dental implant placement in case 2 (f) Twelve months after dental implant placement in case 3. Arrows show the elevated sinus floor. In each case, the implant body was stable without inflammatory findings.

Oven (Yamato Scientific, Tokyo, Japan). The clinical batches were prepared aseptically. Five pieces of the molded OCP/Col were placed in a sterilized micro centrifuge tube, and the tube containing OCP/Col was then packed into an aluminum pouch. The packed OCP/Col was subsequently sterilized using electron beam irradiation (22 kGy) to render it ready for use. After sterilization, the XRD pattern derived from OCP/Col included a collapsed and reduced primary (100) peak with a shift from 4.7 to 5.3 degrees at 2θ, as previously reported [20]. OCP/Col has almost 92% porosity and bimodal peaks of 48 μm (main pores) and 0.3 μm (minor pores), and its specific surface area (SSA) was 17.8 m^2/g, as previously reported [31]. The OCP/Col before implantation was scanned with a Microfocus X-ray CT System (Scan Xmate-E090; Comscantecno Co., Ltd., Kanagawa, Japan) with settings of 90 kV and 0.1 mA, and the image data were calculated using a three-dimensional (3D) image analysis system (TRI/3D-Bon; Ratoc System Engineering, Tokyo, Japan) as previously described [26]. OCP/Col itself has little radiopacity, and the Computed Tomography (CT) values of the OCP/Col before implantation ranged from 130 to

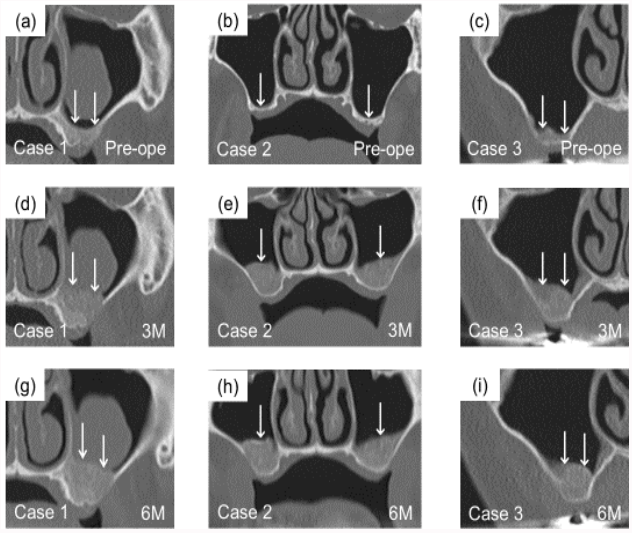

Figure 5: CT images of the coronal plane at 3 and 6 months after OCP/Col implantation. (a-c) Before sinus floor elevation (original sinus) in cases 1, 2 and 3. (d-f) At 3 months after the operation. OCP/Col was detected as hard tissue with radiopacity. (g-i) At 6 months after the operation. The shape of radiopacity was stable in each case, and the radiopacity had increased relative to that at 3 months. The heights of hard tissue at the area of implanted OCP/Col were almost the same as at 3 months, with no signs of absorption. There was a mucous cyst in the sinus in case 1 before OCP/Col implantation.

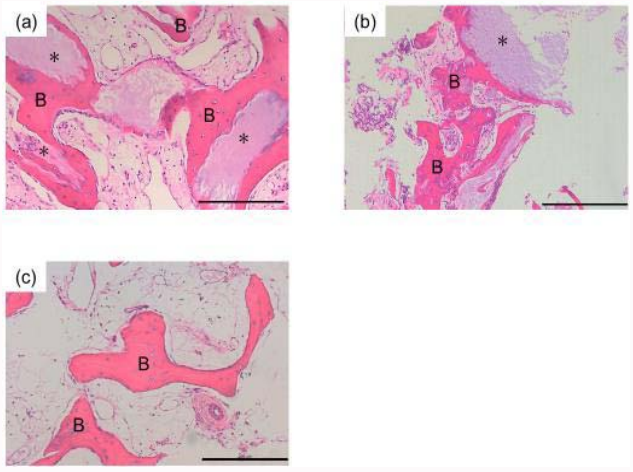

Figure 6: Magnified view of the specimens stained by hematoxylin and eosin. (a) Case 1 (b) Case 2 (c) Case 3. Newly formed bone was observed around remaining granules of OCP/Col. Neither scar tissue nor inflammatory cell infiltration were seen. Bar=200 μm* =remaining implants. B=newly formed bone.

140 Hounsfield Units (HU) [26].

Design of the clinical trial

The current study was a part of the 'Bone Augmentation by Octacalcium Phosphate Collagen Composite' clinical trial, and a part of the 'Prospective, Multi-center, Single-arm Study of OCP/Col for Guided Bone Regeneration' clinical trial, which were registered with the Medical Information Network in Japan (UMIN; registration numbers JPRN-UMIN000015852 and JPRN-UMIN000018192, respectively). The protocol of the former trial was approved by the Research Ethics Committee of Tohoku University Graduate School of Dentistry under reference number [25,26]. This clinical trial was a single-arm non-randomized intervention study. The principal investigator and promoter was Dr. Tadashi Kawai (D.D.S, Ph.D), and this study was performed at the Dept. of Oral and Maxillofacial Surgery, in Tohoku University Hospital, in Sendai, Japan. The protocol of the latter clinical trial was approved by the Institutional Review Board of the Pharmaceuticals and Medical Devices Agency in Japan under reference number OCTC-14001. The sponsor of that clinical trial was Toyobo CO, LTD, and it was a single-arm non-randomized intervention study performed at 9 hospitals in Japan. The aim of the first clinical evaluation in these clinical trials was to assess the safety of the use of OCP/Col to fill bone defects after sinus floor elevation via clinical examinations and analysis of adverse events. The second clinical evaluation was focused on bone regeneration assessment via radiographic and histological examinations. All patients included in the current study provided informed written consent.

Clinical cases

The present study describes the treatment of 3 cases of atrophic posterior maxilla at Tohoku University Hospital. A 41-year-old male Japanese patient (case 1), a 68-year-old male Japanese patient (case 2) and a 54-year-old female Japanese patient (case 3) with nothing noteworthy in their medical records were referred to our hospital for dental implant treatment in the maxilla region. As dental implant placement was impossible because bones in their maxillae were very thin, bone augmentation with a sinus floor elevation technique was necessary before dental implant placement. The respective operative sites of cases 1, 2 and 3 were the left maxillary sinus, bilateral maxillary sinuses and right maxillary sinus (Figure 2a-2c). We performed sinus floor elevation under local Anesthesia in case 1 and 3, and general anaesthesia in case 2. Gingiva and periosteum were ablated and an oval-shaped groove was formed in the lateral wall of the maxillary sinus. Sinus membrane was ablated from the sinus floor, and the membrane was lifted upward with the oval-shaped bone of the lateral wall region (Figure 3a). There was no perforation of the sinus membrane in any of the cases. OCP/Col discs were placed in the space (Figure 3b), and then the gingiva and periosteum were repositioned and sutured.

Clinical and radiographic examination

Clinical examinations involved observation of general and local conditions including inflammatory symptoms at the operative sites. In addition, laboratory examination was carried out. Radiographic and clinical examinations were performed prior to the operations, and 1 day, 7 days, and 1, 3 and 6 months after OCP/Col implantation.

CT scans were performed before the operation and 3 and 6 months after OCP/Col implantation. Coronal scans of the surgical site were obtained using a CT scanner (Somatom Definition flash, Siemens, Germany) at a tube current of 35 mA, a tube voltage of 120 kV and a slice thickness of 0.6 mm. The scanner was calibrated every working day, using a water phantom. The regions of interest (ROIs) were defined at the center of the augmented region. Each ROI was circular and 5 mm in diameter. The HU values of the ROI were measured using software (We View Open-Pacs series, Hitachi Medical Corp, Tokyo, Japan) and all values were reported as mean ± Standard Deviation (SD).

Dental implant placement

After confirmation of bone augmentation by CT at 6 months, dental implant placement was performed under local anaesthesia. Gingiva and periosteum were ablated and dental implant bodies were inserted into the maxillary region. The Dental implant systems were the Astra Tech Implant System, OsseoSpeed™; Dentsply Sirona Inc.,

Table 1: CT values in each case at 3 and 6 months after OCP/Col implantation. All values represent mean ± SD. CT value of the OCP/Col before implantation ranged from 130 HU to 140 HU. CT values increased to approximately 300 HU to 400 HU that was almost the same as cancellous bone.

Region	Case 1	Case 2		Case 3
	Left maxilla	Right maxilla	Left maxilla	Left maxilla
3 Months	260.59 ± 56.99	253.17 ± 63.44	278.72 ± 44.62	178.15 ± 121.64
6 Months	353.78 ± 78.10	317.84 ± 160.89	332.70 ± 145.31	289.85 ± 91.73

Tokyo, Japan or the Straumann® Bone Level Implant; Straumann Japan Inc, Tokyo, Japan.

Histological examination and FTIR analysis

At the time of the dental implant placement operation, samples of newly formed bone were collected from sites where dental implants were going to be inserted, using a trephine bar with a diameter of 2.4 mm in each case. The samples were fixed with 4% para formaldehyde in 0.1 M phosphate-buffered saline, pH 7.4 for a few days, and decalcified in 10% ethylenediaminetetraacetic acid in 0.01 M phosphate buffer, pH 7.4, for 2-4 weeks at 4°C. The samples were dehydrated in a graded series of ethanol concentrations and embedded in paraffin. Each sample was then sectioned at a thickness of 5 mm. The sections were stained with hematoxylin and eosin, and photographs were taken with a photomicroscope (Leica DFC290 HD, Leica Microsystems Japan, Tokyo, Japan). One sample of case 1 was immediately washed in deionized water, lyophilized and reduced to powder. The FTIR spectrum was obtained by a JASCO FT/IR-6300 (JASCO, Tokyo, Japan), with the sample diluted with KBr over a range of 4000–400 cm^{-1} with a 4-cm^{-1} resolution.

Results

Clinical examination

Although swelling and redness at the operative region were observed after several days, the severity of these symptoms was approximately equal to that seen after a normal operation, and disappeared within 7 days in all cases. Laboratory examination indicated increases in C-Reactive Protein (CRP) or White Blood Cells (WBCs) the day after implantation, but these parameters recovered normal levels within 7 days in all cases. The wound healed well and there was no outflow of OCP/Col. Postoperative wound healing was satisfactory, and there were no postoperative infections or allergic reactions at the operative site during the observation period. At the time of dental implant placement surgery, hard tissue was confirmed in the lateral window region (Figure 3c). There were no abnormalities or any inflammation at the time of the second dental implant surgery for the exchange of abutments approximately 6 months later. After that, a final prosthesis was placed and occlusion was reconstructed (Figure 3d). Each patient had a different type of prosthesis fitted, and the three types were an implant bridge, an implant over denture and an implant crown.

Radiographic examination

In radiographic examination, the thickness of bone from the alveolar crest to the sinus floor in the left maxillary region in case 1 was almost 5 mm before OCP/Col implantation. In case 2, that of bilateral maxillaries was 1 mm to 2 mm, and that of case 3 was 5 mm. Radiopacity was not observed at the operated region the day after OCP/Col implantation in any of the cases, because OCP/Col has little radiopacity (Figure 4a). However, radiopacity had appeared at the area of implanted OCP/Col and the sinus floor had become unclear at 3 months (Figure 4b). At 6 months, the radiopacity had further increased and was almost equal to that of surrounding bone.

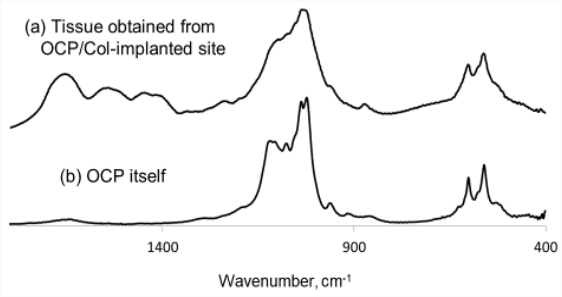

Figure 7: FTIR spectra of (a) tissue obtained from OCP/Col-implanted site, and (b) OCP itself. IR spectral bands at approximately 1030-1130 cm^{-1} changed to those of HA in tissue obtained from OCP/Col-implanted site. The features of CO_3^{2-} were confirmed at bands at approximately 870 and 1410-1460 cm^{-1} in the spectra of the specimen.

The sinus floor had become clear and was augmented (Figure 4c). Radiopacity was stable at 12 months after dental implant placement with the final prosthesis (Figure 4d-4f).

Figures 5a-5c show CT pictures of the 3 cases before OCP/Col implantation. Mucous cyst was confirmed in the sinus of case 1 before sinus floor elevation. At 3 months after OCP/Col implantation, a coronal CT view indicated radiopacity at the area of implanted OCP/Col in the sinus (Figure 5d-5f). At 6 months, radiopacity had further increased (Figure 5g-5i). The heights of hard tissue at the area of implanted OCP/Col were almost the same, with no signs of absorption. In case 1, the respective CT values of the augmentation region at 3 and 6 months were 260.59 ± 56.99 and 353.78 ± 78.10. Those of case 2 were 253.17 ± 63.44 and 317.84 ± 160.89 in the right maxillary sinus and 278.72 ± 44.62 and 332.70 ± 145.31 in the left maxillary sinus. Those of case 3 were 178.15 ± 121.64 and 289.85 ± 91.73 (Table 1).

Histological examination and FTIR analysis

Figure 6 shows the alveolar crest biopsy specimens from each case. Newly formed bone was observed around remaining granules of OCP/Col (Figure 6a-6b). In case 3, there was no remaining OCP around bone tissue (Figure 6c). Neither scar tissue nor inflammatory cell infiltration were seen. Figure 7 shows the FTIR spectra of the specimen of case 1 and OCP itself. The features of FTIR spectra of the specimen indicate conversion of OCP/Col into HA in the IR spectral bands around 1030–1130 cm^{-1}. The features of CO_3^{2-} were confirmed at bands around 870 and 1410–1460 cm^{-1} in the spectra of the specimen. The specimen did not exhibit any of the characteristic features of OCP.

Discussion

Various materials are currently used as bone substitute materials in dental implant treatment and its effectiveness has been reported [3,14,15], although they are inferior to autologous bone. Many studies have been performed with the aim of improving osteoconductivity by combining these materials [32], or incorporating other factors [33] or mesenchymal stem cells [34]. Today, other groups have reported

superior bone regeneration via the mixing of autologous bone and artificial material [35]. However, the results in this study provide evidence of a single material, OCP/Col, with high osteoconductivity and effectiveness for dental implant treatment.

In this study, OCP/Col was applied in conjunction with sinus floor elevation, in 4 maxillary sinuses of 3 patients. Previous studies demonstrated that there was no abnormality such as infection or inflammation in 10 patients in whom OCP/Col was applied as a treatment for defects caused by cystectomy or tooth extraction [28]. Likewise, the abnormality finding that was apparent to 3 patients in the current study was not confirmed. Thus, it has been suggested that OCP/Col is safe for clinical use in humans. OCP/Col consists of cross-linked collagen, so it was easy to use OCP/Col in the operative region without it collapsing, and OCP/Col was stable in the space because the collagen adhered to living tissue well. Therefore, it was considered that OCP/Col could be applied to a case of small perforation of the sinus membrane that was a surgical complication of sinus floor elevation [36]. Usually in such a case, an absorbent membrane sheet product is used to cover the perforated region, and bone substitute materials are placed in the created space, or the operation is terminated [37]. However, OCP/Col could cover the perforated region if the size was small, and function as a bone substitute by itself.

OCP/Col converted to hard tissue over time, as determined radio graphically. In this study, this phenomenon made it easy to confirm bone augmentation via dental radiography. At 3 months, radiopacity was observed at the OCP/Col region and it had become clear by 6 months in all sinuses. Furthermore, there was little change even at 12 months after dental implant placement. CT pictures showed radiopacity at the OCP/Col region at 3 or 6 months. The heights of augmentation of each sinus were almost maintained without absorption, and the border between the host bone of maxilla and hard tissue formed via OCP/Col became unclear within 6 months. CT values indicated increasing over time. The CT value of OCP/Col is approximately 130 HU to 140 HU. At 3 months, the CT values of each sinus increased to approximately 200 HU to 300 HU, and furthermore, these values tended to be increased at 6 months, to approximately 300 HU to 400 HU. The values at 6 months were similar to that of cancellous bone. The SDs of CT values were substantial at approximately 100 in each sinus. The inside of the maxilla comprised cancellous bone that included a sparse part. Therefore, it was thought that the bone that was newly formed via OCP/Col was similar to the cancellous bone of the maxilla, as indicated by the SDs of the CT values in this study.

Previous studies have demonstrated that OCP/Col converted to normal bone tissue after implantation in rat and dog bone defects [22]. In the current study, the conversion of OCP/Col to normal bone tissue was confirmed histological in humans for the first time. Furthermore, there was no infiltration of inflammatory cells around bone that was newly formed via OCP/Col. Some remaining granules in newly formed bone were detected histological. However, the features of FTIR spectra indicated the conversion of OCP of OCP/Col into biological apatite, and the characteristic features of OCP were not apparent. These results demonstrated that normal bone tissue was formed around remaining granules and OCP of OCP/Col could be converted to biological apatite without the OCP itself remaining, as has been observed in prior animal studies [22,23,38].

It has been approximately 12-18 months since final dental implant placement in the 3 cases, and no substantial adverse events have occurred. The dental Implant treatment of these 3 cases was performed to the point of final prosthesis fitting without any problems. The final prosthesis was different in each case, the three types being an implant bridge, an implant over denture, and an implant crown, and there were no problems with any of the prostheses. There was no secondary operative site for bone grafting due to the use of OCP/Col instead of autogenous bone, and each case exhibited good progress. The period of dental implant treatment from bone augmentation to final prosthesis was almost the same as that associated with the use of autogenous bone. This study demonstrated that OCP/Col application for bone augmentation before dental implant placement was effective, and that it was safe to use OCP/Col in humans. Furthermore, it was suggested that OCP/Col could be applied to other cases of bone defect or atrophy in the field of oral and maxillofacial surgery.

Conclusion

The present study suggested that octacalcium phosphate collagen composite could be applied to bone augmentation in conjunction with sinus floor elevation for maxillary atrophic patients, and that octacalcium phosphate collagen composite could be converted to normal bone tissue in humans.

Acknowledgement

This clinical trial (JPRN-UMIN000015852) was conducted as a collaborative investigation with Toyobo. Co, Ltd. Company (project code: J140002441). Another clinical trial (JPRN-UMIN000018192) has also been conducted by the same company.

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