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Human Dentin as Novel Biomaterial for Bone Regeneration

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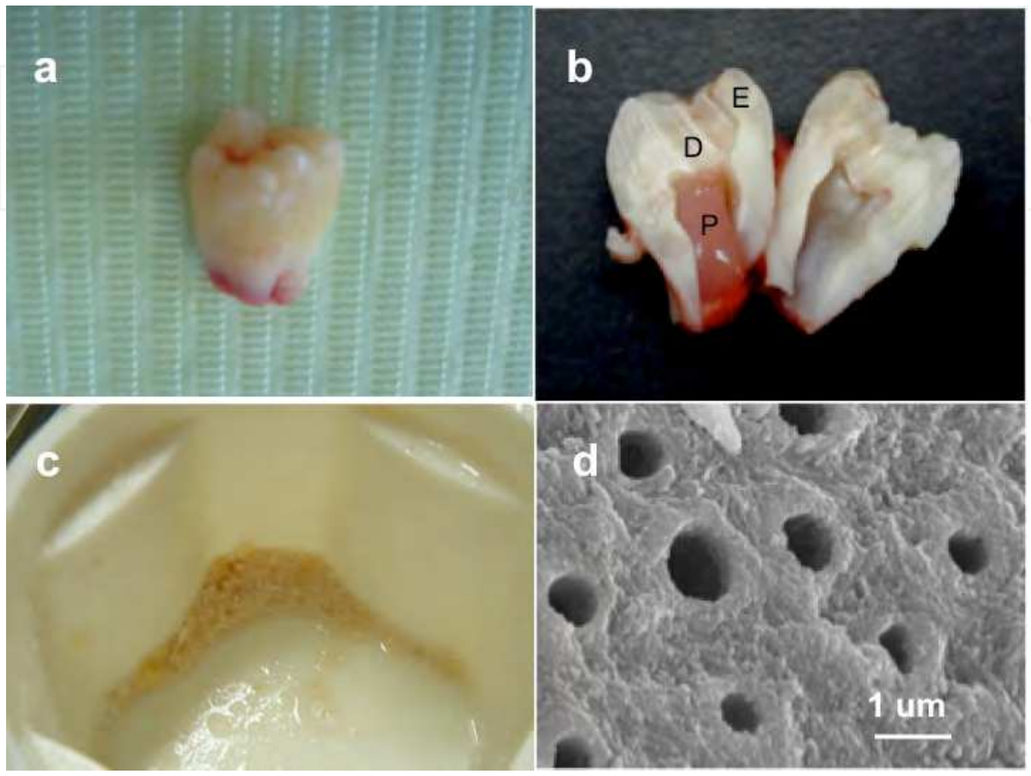
1. Introduction

Human dentin autograft was reported in 2003 as a first clinical case (Murata et al., 2003), while human bone autograft was done in 1820. There was a long-long time lag between the autografts of dentin and bone. In 2009, Korea Tooth Bank was established in Seoul for the processing of the tooth-derived materials in Seoul, and an innovative medical service has begun for bone regeneration. Recently, the tooth-derived materials have been becoming a realistic alternative to bone grafting.

The regeneration of lost-parts of the skeleton has been generally carried out with fresh, autogenous bone as a gold standard. To obviate the need for harvesting of grafts and thus, to avoid morbidity resulting from it, the researches for bone substitutes (Kuboki et al., 1995; Asahina et al., 1997; Takaoka et al., 1991; Artzi et al., 2004; Kim et al., 2010) or bone production via bio-engineering have begun (Wozney et al., 1988; Wang et al., 1990; Murata et al., 1999). In the regenerative field, there is a medical need for biomaterials that both allow for bone formation and also gradually absorb as to be replaced by bone. Non-absorbable materials are never replaced by bone and thus, reveal chronic inflammation in tissues as foreign bodies.

As bone and dentin consist of fluid (10%), collagen (20%) and hydroxyapatite (70%) in weight volume, our attention for biomaterials is collagenous and ceramic materials (Murata et al., 2000; Murata et al., 2002; Akazawa et al., 2006; Murata et al., 2007). Generally, extracted teeth have been discarded as infective medical dusts in the world. We have thought the non-functional teeth as native resource for self and family (Fig. 1). Therefore, we noticed on bone-inductive, absorbable properties of dentin, and have been studying a medical recycle of human teeth as a novel graft material for bone regeneration in Japan and Korea (Akazawa et al. 2007; Kim et al. 2010). Biomaterial science should support and develop the advanced regenerative therapy using enamel and dentin matrix for patients in the near future.

In this chapter, human dentin will be introduced as novel biomaterial and also as carrier matrix of the recombinant human bone morphogenetic protein-2 (BMP-2) delivery for bone engineering.



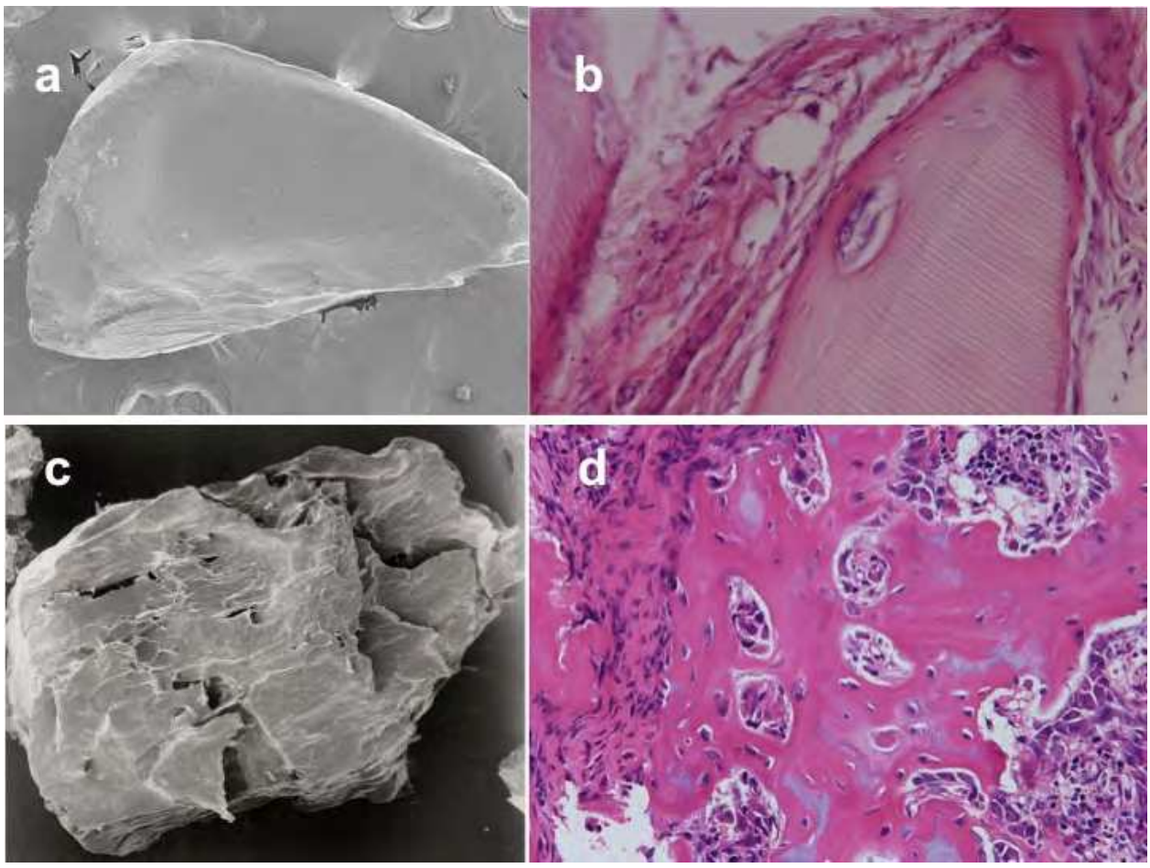
a: whole appearance of molar.
b: divided tooth (E; enamel, D; dentin, P; pulp).
c: crushed tooth granules.
d: SEM photograph of calcified dentin after crushing and washing. Note; dentinal tubes

Fig. 1. Human wisdom tooth

2. Bone induction of human dentin

In 1967, bone-inducing property in rabbit dentin was confirmed in the intramuscular pockets (Yeoman &Urist, 1967; Bang & Urist, 1967), after the discovery of bone induction by rabbit demineralized bone matrix (DBM) in 1965 (Urist, 1965). The rabbit studies reported that completely demineralized dentin matrix (DDM) induced bone at 4 weeks, while non-demineralized dentin (so-called, calcified dentin) induced bone at 8-12 weeks after implantation (Yeoman & Urist, 1967). In our study, human DDM including small patches of cementum derived from wisdom teeth, and human DBM derived from adult femur induced bone and cartilage independently in the subcutaneous tissues at 4 weeks (Murata et al., 2010a). The delayed inductive properties of the calcified dentin and bone may be related to the inhibition of BMP-release by the apatite crystals. Highly calcified tissues such as cortical bone and dentin are not earlier in osteoinduction and bone fornmation than spongy bone, decalcified bone (DBM), and decalcified dentin (DDM) (Huggins et al., 1970).

Dentin and bone are mineralized tissues and almost similar in chemical components. Both DDM and DBM are composed of predominantly type I collagen (95%) and the remaining as non-collagenous proteins including small amount of growth factors (Finkelman et al., 1990). In other words, DDM and DBM can be defined as acid-insoluble collagen binding bone morphogenetic proteins (BMPs), which are member of transforming growth factor-beta (TGF-β) super-family. BMPs were discovered from bone matrix (Urist, 1965; Sampath & Reddi., 1983), and had bone-inducing property in non-skeletal site (Murata et al., 1998). Animal dentin-derived BMPs were extracted with 4M guanidine HCl, and partially purified from rat, rabbit, and bovine (Butler et al., 1977; Urist & Mizutani, 1982; Kawai & Urist, 1989; Bessho et al, 1990). In addition, the concentration of TGF-β, Insulin growth factor-I (IGF-I) and Insulin growth factor-II (IGF-II) were detected in human dentin (DDM). Briefly, the three growth factors were measured in the following concentration (ng/μg 4M guanidine hydrochloride-EDTA protein): TGF-β (0.017), IGF-I (0.06) and IGF-II (0.52). All 3 growth factors were present in concentrations lower than that in human bone (Finkelman et al., 1990). Recently, both mature and immature types of BMP-2 were detected in human dentin and dental pulps (Ito et al., 2008).



a: SEM of DDM (granule size: 0.5mm), Note: smooth surface and no crack.
b: bone induction by DDM at 4 weeks.
c: SEM of DBM (granule size: 0.5mm), Note: micro-cracks and spaces of blood vessels.
d: bone induction by DBM at 4 weeks.

Fig. 2. Dematerialized dentin matrix (DDM) and dematerialized bone matrix (DBM)

Even after the demineralization of dentin, active types of BMPs bind collagen-rich matrices, similar to bone (Urist et al., 1973). The decalcified dentin (DDM) was known to be more active bone-inducing matrix than the calcified dentin (Yeoman & Urist, 1967), and roll type of decalcified dentin membrane revealed better activity of bone induction (Inoue et al., 1986).
Very interestingly, the demineralized treatment for bone and dentin increased their osteoinductivity and decreased their antigenesity (Reddi, 1974). These facts are scientifically very important for the processing procedures of hard tissue-derived graft materials (Kim et al., 2010; Murata et al, 2010a).
The acid-insoluble dentin matrix (DDM) after demineralization is an organic, absorbable material with original dentin structures. Human DDM, prepared from vital teeth-origin, were implanted into the subcutaneous tissue in 4 week-old nude mice, deficient in immunogenic reactions. The DDM induced bone and cartilage independently at 4 weeks after the subcutaneous implantation, similar to human DBM (Murata et al., 2010b). The independent differentiation of bone and cartilage was compatible to our previous study using ceramic and collagen combined with BMPs (Murata et al., 1998). The acid-insoluble collagen, DBM and DDM, possess the ability to coagulate platelet-free heparinized, citrated, and oxalated blood plasmas (Huggins & Reddi., 1973). Clotting constituents become denatured in contact with the insoluble coagulant proteins. The coagulation action of blood plasma by DBM and DDM should become advantageous for surgical operations. Collagenous materials has been commercially available as medical uses for more 30 years.

3. Clinical study of human dentin

3.1 Case 1: Bone augmentation, 48 year-old man

First clinical study was reported at 81st IADR conference, Sweden in 2003 that DDM autograft had succeeded for bone augmentation (Murata et al., 2003).
The aim of this pioneering study is to observe new bone formation in the tissues obtained from the dental implant-placed region after the DDM graft for sinus lifting.

Patient

A 48-year-old male presented with missing teeth (#24-#26, #45-#47). Clinical examinations revealed an atrophied upper jaw in the region (Fig. 3,4). His medical history was unremarkable.

Surgical procedure 1

Four teeth (#17,#18,#25,#28) were extracted and 2 molars (#17,#18) were stocked at -80℃ for DDM. His right occlusion was restored using dental implants as the first clinical step (Fig. 4b).

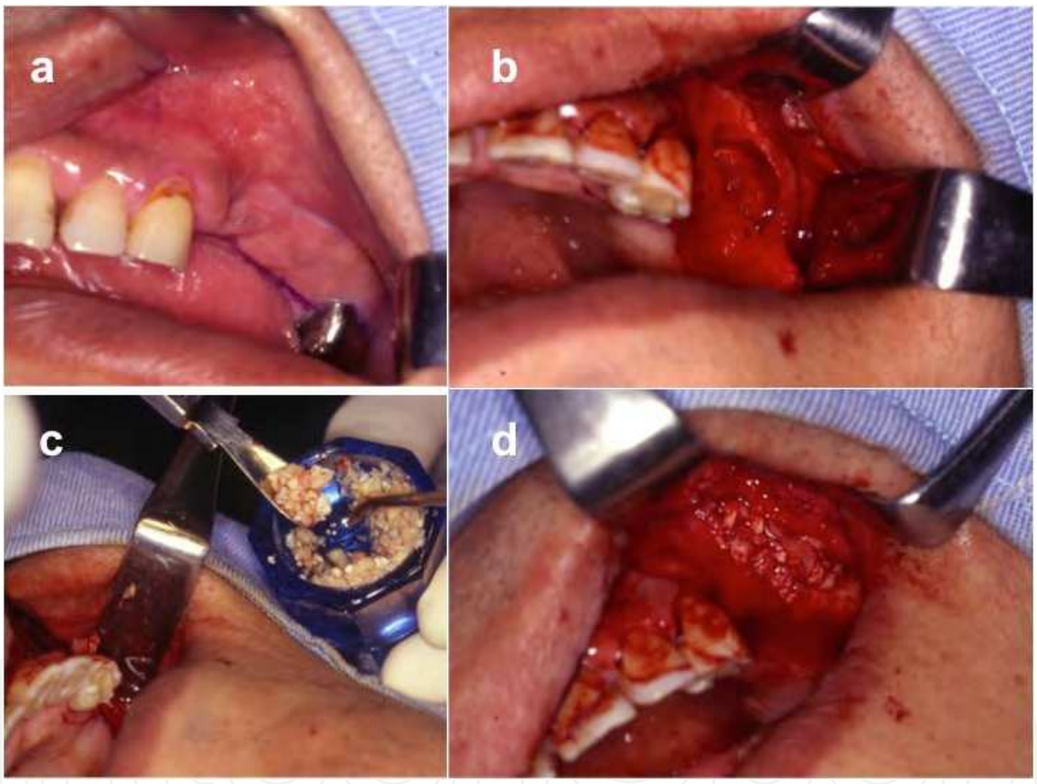
Preparations of DDM

The autogenous DDM were obtained from non-functional vital teeth (#17, #18) (Fig. 4a). The molars were crushed by hand-made under the cooling with liquid nitrogen. The crushed tooth granules were decalcified completely in 0.6N HCl solution. The DDM granules including cementum were extensively rinsed in cold distilled water, and then freeze-dried (Murata et al., 2010a).

Surgical procedure 2

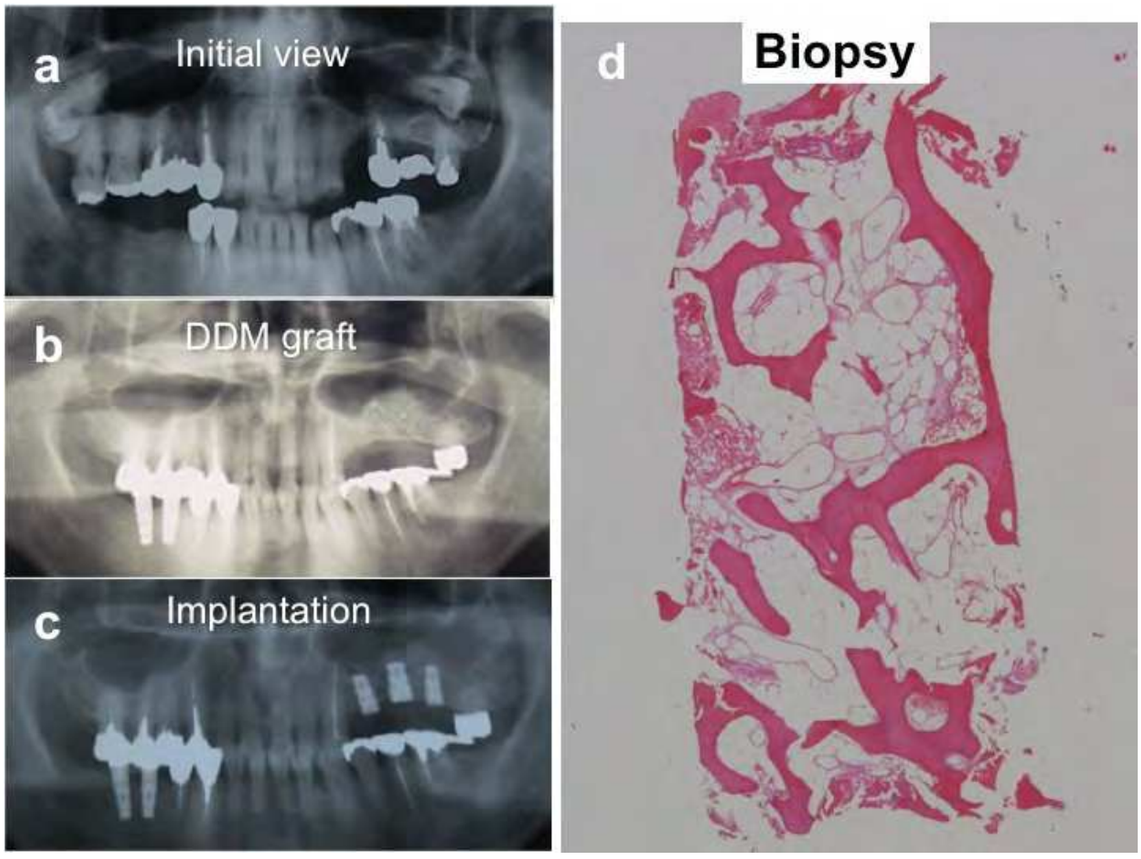
Sinus lifting procedure was done using autogenous dry DDM for bone augmentation (Fig. 3). At 5 months after the operation, 3 fixtures (FLIALIT-2®, FRIADENT) were implanted

into the augmented bone under local anesthesia (Fig. 4c). At the same time, bone biopsy was carried out for the tissue observation (Fig. 4d).



a: intraoral initial view (before operation), Note: 3 missing teeth and atrophied maxilla.
b: oval shaped window
c: autogenous DDM derived from 2 molars
d: view just after DDM autograft

Fig. 3. Case 1: DDM autograft for sinus lifting, 48 year-old man



a: initial view, b: 4 months after DDM graft, c: dental implant placement, d: mature bone with marrow

Fig. 4. X-ray photography and bone biopsy

Results and discussion

The biopsy tissue showed that mature bone was interconnected with the remained DDM granules (Fig. 4d). We found that DDM facilitated its adaption of the grafted site and was slowly absorbed as new bone began to form.

Conclusion

This patient was successfully restored with the dental implants after the DDM autograft. These results demonstrated that autogenous dentin could be recycled as an innovative biomaterial.

3.2 Case 2: Bone regeneration, 58 year-old woman

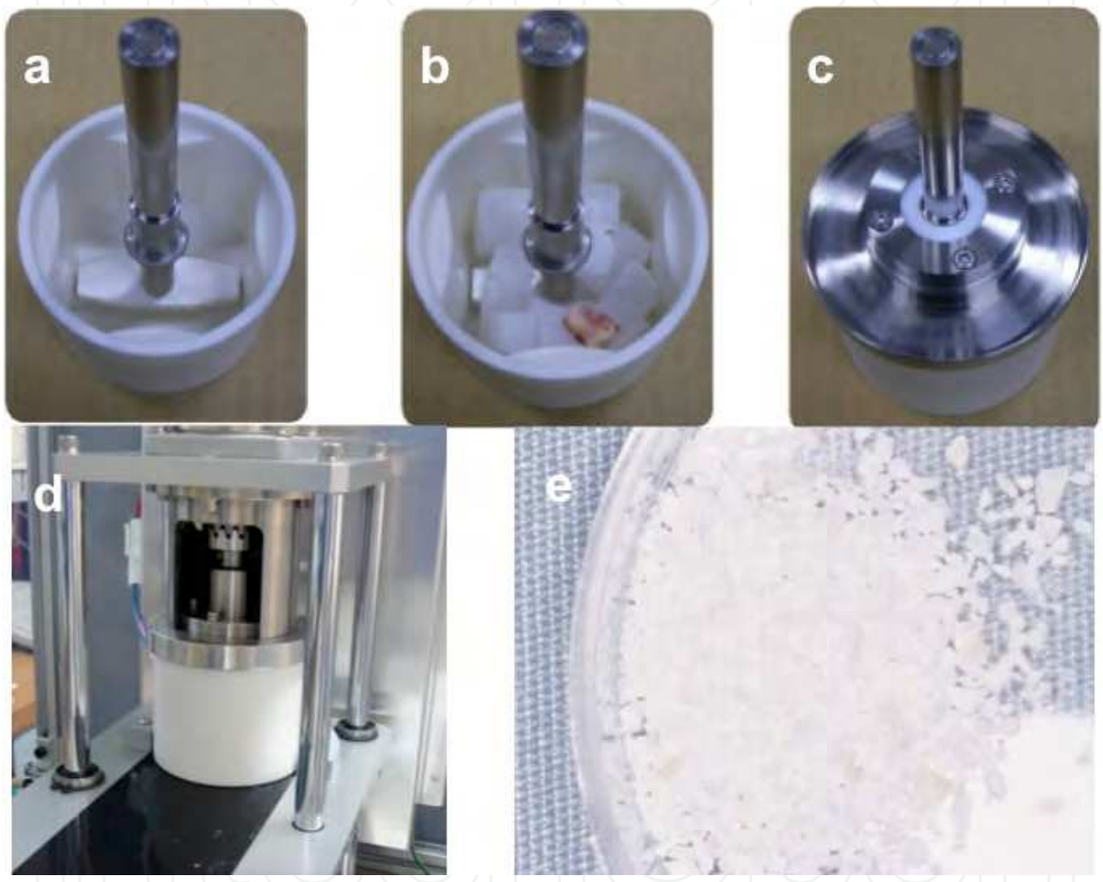
Patient

A 58-year-old female presented with missing teeth (#12-#22). A clinical examination revealed an atrophied upper jaw in the section. Her medical history was unremarkable.

Preparations of DDM

The autogenous DDM were obtained from a non-functional vital tooth (#17). The second molar was crushed with saline ice by our newly developed tooth- mill (DENTMILL®, Tokyo Iken Co., Ltd) at 12000rpm for 30 sec (Fig. 5). Briefly, vessel and blade were made in ZrO_2 ,

which have gained the approval of Food and Drug Administration (FDA) for human use. The ZrO_2 ceramics were fabricated by sintering at 1400℃ for 2 h after the slip casting of the mixture of ZrO_2 powder and distilled water (Fig. 5a). As the results of characteristics analyses of ZrO_2 objects, the contraction rate, the relative density, and the bending strength were 21%, 99%, and 400MPa, respectively. The automatic mill could crush a tooth and/or a cortical bone block (1x1x1cm^3) under the condition of cooling using saline ice blocks (1cm^3) (Fig. 5b). The crushed tooth granules were decalcified completely in 0.026N HNO_3 solution for 20 min. The DDM granules including cementum were extensively rinsed in cold distilled water (Fig. 5e), (Murata et al., 2009; Murata et al., 2010a).



a: ZrO_2 vessel and blade, b: tooth with ice blocks, c: stainless cover, d: mill, e: DDM granules before clinical use.

Fig. 5. Preparation of DDM using automatic tooth mill (DENTMILL®, Tokyo Iken)

Surgical procedure

Splitting osteotomy and cortical perforations were performed in the atrophied jaw and the autogenous DDM were transplanted to the treated bone in 2006 (Fig. 6a,b,c). At 4 months after the operation, 3 same fixtures (Synchro-steppted screw type: diameter; 3.4mm, length; 11mm, FLIALIT-2® , FRIADENT) were implanted into the augmented bone under local anesthesia (Fig. 6b). At the same time, bone biopsy was carried out for the tissue observation.

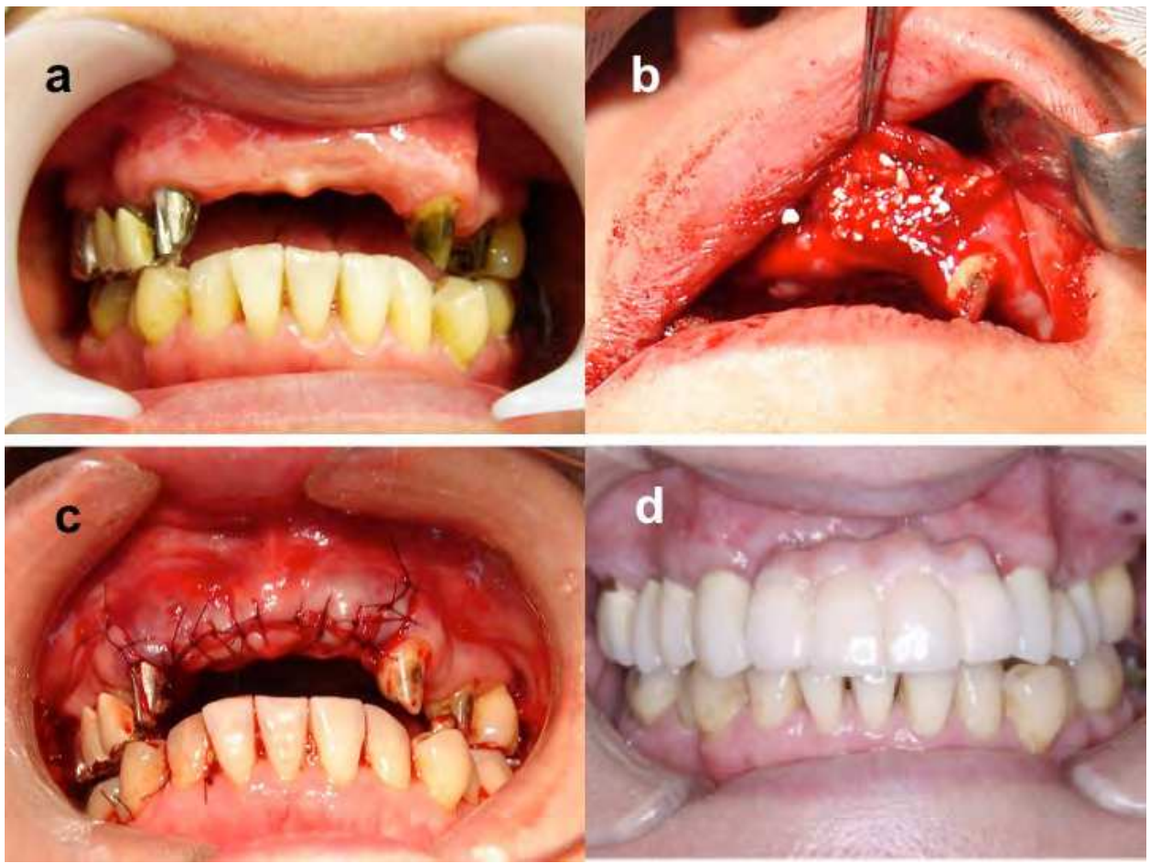
Results and discussion

The biopsy tissue showed that DDM granules were received to host and the biological width (4-6mm) was acquired. The DDM residues were partially observed during the implant placement. Bone biopsy revealed the DDM were remodeled by bone at 4 months. This patient was successfully restored with the dental implants after the DDM autograft (Fig. 6d). Though animal-derived atelocollagens have been generally used as medical materials, autogenous decalcified dentin is a highly insoluble collagenous matrix and a safe biomaterial.

Conclusion

Human DDM granules from vital teeth are collagenous matrics with osteoinductive potency, and the human dentin can be recycled as autogenous biomaterials for local bone engineering.

Case 1 and 2 were approved by the Ethical Committee in the Health Sciences University of Hokkaido. All subjects enrolled in this research have responded to an Informed Consent which has been approved by my Institutional Committee on Human Research and that this protocol has been found acceptable by them.



a: 4 missing teeth and atrophied upper maxilla b: DDM autograft before suture c: just after operation d: final view after prosthetic restoration using dental implantation

Fig. 6. Case 2: Bone regeneration, 58 year-old woman

4. Dentin scaffold for recombinant human BMP-2

4.1 Recombinant human BMP products

BMP-2, 4, and 7 are strong accelerating factors of bone induction. Currently, BMP-2 and BMP-7 have been shown in clinical studies to be beneficial in the therapy of a variety of bone-related conditions including delayed union and non-union. BMP-2 (Medtronic Co.Ltd.) and BMP-7 (Stryker Biotech Co.Ltd.) have received Food and Drug Administration (FDA) approval for human clinical uses (fractures of long bones, inter-vertebral disk regeneration), by delivery in purified collagen matrix or ceramics. Moreover, the BMP-2 product has been approved for certain dental applications. BMP-7 has also found use in the treatment of chronic kidney disease. In 2002, Curis licensed BMP-7 to Ortho Biotech Products, a subsidiary of Johnson & Johnson.

4.2 Acceleration of bone induction by BMP2 in human DDM scaffold

The aim of the following study was to estimate the increase of the bone-inductive potency by DDM combined with BMP-2 in rat subcutaneous tissues.

Composition of BMP-2 solution and DDM

One hundred micro-liter of recombinant human BMP-2 solution (0.0, 0.5, 1.0, 2.0, 5.0μg of BMP-2) was mixed with 70 mg of human DDM in a sterilized syringe. The composite was called as the BMP-2/DDM. The DDM alone with 100μl of PBS was also prepared as a BMP-free control.

Bioassay in rats

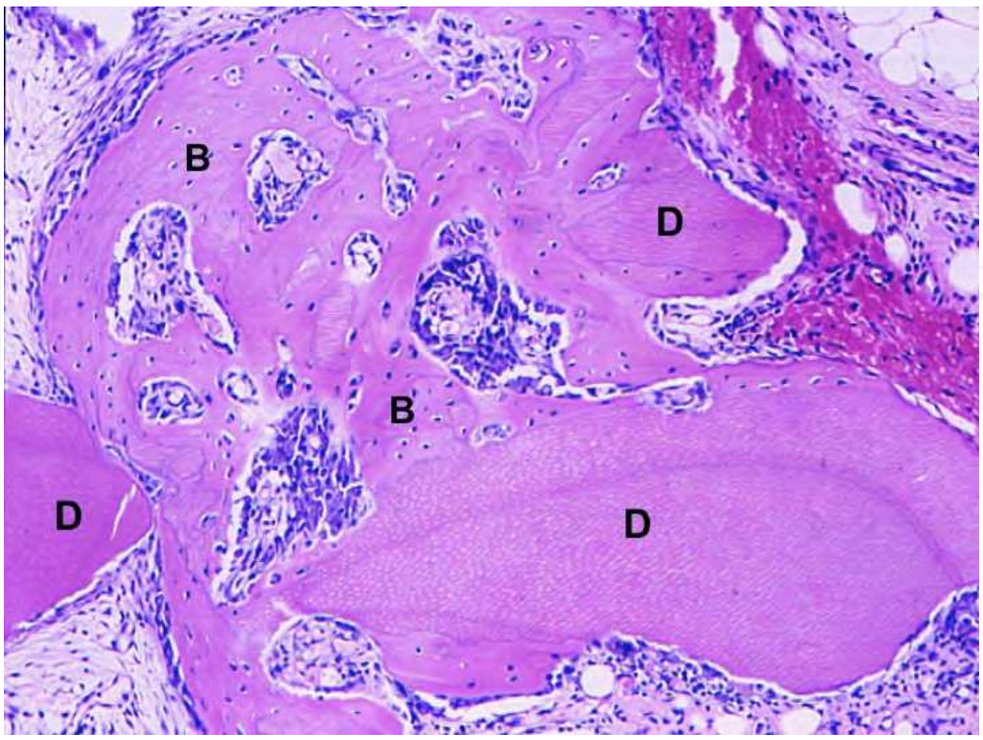
Wistar rats (male, 4 week-old) were subjected to intraperitoneal anesthesia and incisions were added to the back skin under the sterile conditions. Each animal received three BMP-containing composites (BMP-2/DDM) and one BMP-free control (DDM alone). The implanted materials were removed at 3 weeks after implantation, and prepared for histomorphological examinations. All procedures were followed the Guidelines in Health Sciences University of Hokkaido for Experiments on Animals.

Histological findings and Morphometric analysis at 3 weeks

In the BMP-2 (5.0μg)/DDM (70mg) group, bone with hematopoietic bone marrow developed extensively at 3 weeks. Chondrocytes were found only in the BMP-2 (0.5, 1.0μg)/DDM groups (Table 1). The BMP-2 (2.0, 5.0μg)/DDM groups accelarated bone induction predominantly (Fig. 7). In the DDM alone group, mesenchymal tissue was seen between DDM particles, and hard tissue induction was not observed at 3 weeks (Fig. 8). Morphometric analysis demonstrated that the volume of the induced bone and marrow increased at BMP-2 dose-dependent manner, while the DDM decreased at the dose-dependent (Table 1). Briefly, the volume of the bone and marrow in BMP-2 (1.0μg)/DDM and BMP-2 (5.0μg)/DDM showed 3.7% and 26.3%, respectively. BMP-2 (0.5μg)/DDM showed 0.0% and 4.0% in the volume of bone and cartilage, respectively.

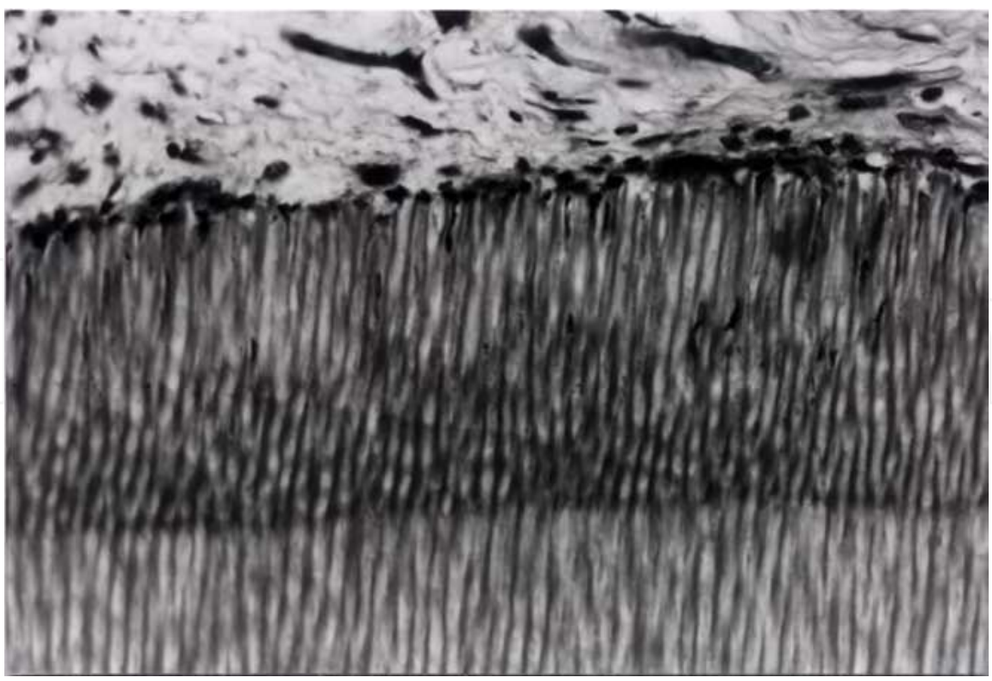
Conclusion

BMP-2 strongly accelerated bone formation in the DDM carrier system. DDM never inhibited BMP-2 activity and revealed better release profile of BMP-2. These results indicate that human recycled DDM are unique, absorbable matrix with osteoinductivity and the DDM should be an effective graft material as a carrier of BMP-2 delivering and a scaffold for bone-forming cells for bone engineering.



Induced bone (B) bridging between DDM (D) granules. Note: active osteoblast differentiation.

Fig. 7. Photograph in BMP-2 (5.0µg)/DDM (70mg) at 3 weeks



Fibroblasts on surface of DDM granule with original dentinal tubes.

Fig. 8. Photograph in DDM (70mg) alone at 3 weeks

	Dose of BMP-2 (μg)				
	0	0.5	1	2	5
bone	0	0	3.7 ± 1.41	7.4 ± 0.94	20.3 ± 4.64
cartilage	0	4.0 ± 0.81	2.3 ± 0.47	0	0
bone marrow	0	0	0	0	6.0 ± 1.63
DDM	57.0 ± 0.81	43.3 ± 3.39	41.0 ± 2.16	40.3 ± 1.69	37.0 ± 0.81
mesenchymal tissue	40.7 ± 0.94	49.0 ± 5.09	48.0 ± 3.85	46.0 ± 2.16	32.7 ± 5.73
connective tissue	2.3 ± 0.47	3.7 ± 1.24	5.0 ± 0.47	6.3 ± 0.47	4.0 ± 0.81
All tissue: 100 % , values: mean ± SD , N: 9, Explanted time: 3 weeks					

The volume of bone and marrow showing a dose-dependent increase.
The volume of DDM showing a dose-dependent decrease.

Table 1. Morphometry of BMP-2 dose-dependent study.

5. Material science for patients in the near future

Biomaterials have had a major impact on the regenerative medicine and patient care for improving the quality of lives of human.

We have been challenging to be able to develop bioabsorbable materials, harmonized with living body, especially bone remodelling, using an innovative supersonic and acid-etching technology (Akazawa et al. 2010). Implanted biomaterials first contact to body fluid and cells. Human cells never live in dry condition. Generally, organ and tissue have interconnected porous structure for dynamic flow of body fluid. Material walls inhibit the body fluid permeation and the cell invasion. Therefore, we focused on the permeability of body fluid into the bulk of materials and the biomimetic structure for the living and working cells (Murata et al., 2007). Body fluid can permeate into collagenous materials such as DDM and DBM. Novel DDM material contains native growth factors, and adsorbs several proteins derived from body fluid. In addition, DDM with RGD sequences supports mesenchymal cell adhesion as anchorage matrix.

Most importantly, material scientists, engineers, and doctors must work together and cooperate as professionals for the development of functional materials and for the present and future of all patients.

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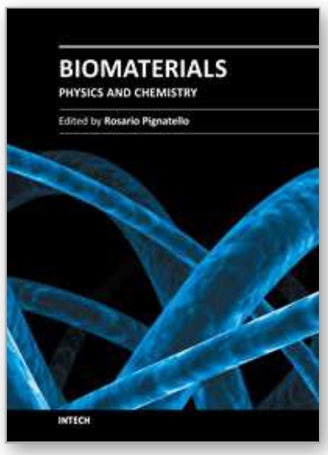
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These contribution books collect reviews and original articles from eminent experts working in the interdisciplinary arena of biomaterial development and use. From their direct and recent experience, the readers can achieve a wide vision on the new and ongoing potentialities of different synthetic and engineered biomaterials. Contributions were selected not based on a direct market or clinical interest, but based on results coming from very fundamental studies. This too will allow to gain a more general view of what and how the various biomaterials can do and work for, along with the methodologies necessary to design, develop and characterize them, without the restrictions necessarily imposed by industrial or profit concerns. The chapters have been arranged to give readers an organized view of this research area. In particular, this book contains 25 chapters related to recent researches on new and known materials, with a particular attention to their physical, mechanical and chemical characterization, along with biocompatibility and hystopathological studies. Readers will be guided inside the range of disciplines and design methodologies used to develope biomaterials possessing the physical and biological properties needed for specific medical and clinical applications.

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