



Dental alloplastic bone substitutes currently available in Korea

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Abstract (J Korean Assoc Oral Maxillofac Surg 2019;45:51-67)

As dental implant surgery and bone grafts were widely operated in Korean dentist, many bone substitutes are commercially available, currently. For commercially used in Korea, all bone substitutes are firstly evaluated by the Ministry of Health and Welfare (MOHW) for safety and efficacy of the product. After being priced, classified, and registration by the Health Insurance Review and Assessment Service (HIRA), the post-application management is obligatory for the manufacturer (or representative importer) to receive a certificate of Good Manufacturing Practice by Ministry of Food and Drug Safety. Currently, bone substitutes are broadly classified into C group (bone union and fracture fixation), T group (human tissue), L group (general and dental material) and non-insurance material group in MOHW notification No. 2018-248. Among them, bone substitutes classified as dental materials (L7) are divided as xenograft and alloplastic bone graft. The purpose of this paper is to analyze alloplastic bone substitutes of 37 products in MOHW notification No. 2018-248 and to evaluate the reference level based on the ISI Web of Knowledge, PubMed, EMBASE (1980-2019), Cochrane Database, and Google Scholar using the criteria of registered or trademarked product name.

Key words: Bone substitutes, Dental implantation, Korea

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I. Introduction

As dental implant surgery for edentulous patients became a gold standard, bone grafts such as guided bone regeneration and sinus lift were widely operated in Korean dentist. There has been increased in the number of bone substitute products available to the dental clinician. Still the autologous bone is considered to gold standard, because of its three properties with osteoconduction, osteoinduction and osteogenesis. Osteogenesis is, the property of autogenous graft, generation

of new bone from osteogenic cells within the graft. Osteoinduction is the property of the autogenous graft, allogenic graft and intrinsic bone matrix proteins such as transforming growth factor and bone morphogenetic proteins (BMP) to recruit of host stem cells. Osteoconduction is the property of a mechanical structure with biocompatibility for the migration of osteogenic cells^{1,2}.

Allograft has been widely used and is an attractive alternative as it avoids donor site morbidity. It has the following advantage: (1) donor site is not needed, (2) abundant supply, and (3) little risk of transmission of infectious diseases³. The ideal alloplastic bone substitutes is biologically stable and maintain its volume with allowing cell infiltration and remodeling process⁴. The alloplastic bone substitutes has various osteoconductive capabilities depending on the manufacturing methods, crystal structure, size of pores, mechanical properties, composition and absorption rate⁵.

Hydroxyapatite (HA) is the main mineralized of bone tissue and it exerts an osteoconductive ability when grafted in the defect. Synthetic calcium phosphate ceramics (β -tricalcium

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phosphate [β -TCP] and HA) could be altered to autogenous graft, allogenic graft and xenogenic graft and it was used as block, cement, pastes, powder, granules and putty type with carboxymethyl cellulose or hyaluronic acid⁶. In Korea, the development of implant dentistry has led to the development of many dental synthetic bone substitute in many domestic companies.

As dental implant surgery for edentulous patients became a gold standard, bone grafts such as guided bone regeneration and sinus lift were widely operated in Korean dentist. All bone substitutes used commercially in Korea are firstly evaluated by the Ministry of Health and Welfare (MOHW) for safety and efficacy of the product. They are commercialized after being priced, classified, and registration by the Health Insurance Review and Assessment Service (HIRA). The post-application management is obligatory for the manufacturer (or representative importer) to receive a certificate of Good Manufacturing Practice (GMP) by Ministry of Food and Drug Safety (MFDS).

According to Korea Food and Drug Safety (KFDS) No. 2016-156 of ‘medical device manufacturing and quality control standards’, after the approval of commercially use, the manufacturer or importer is required to renew the conformity certification every three years or immediately if the information of product changed⁷. If any information of the product changed, the certificate of conformity should be issued or re-issued by the manufacturer or the importer. Therefore, the manufacturer or importer of registered in the MFDS could be important factors in terms of quality control of currently available bone substitutes.

However, it is difficult for clinicians to know whether the certification or the quality of product is properly managed. Therefore, the purpose of this study is to analyze ingredients, manufacturers, importers, current status and reference levels of dental synthetic bone listed in MOHW notification No. 2018-248.

II. Materials and Methods

Commercially available dental alloplastic bone substitute which was approved MOHW notification (No. 2018-248)⁸ is analyzed the details of manufacturer, importer, composition, available form, Food and Drug Administration (FDA, USA) approval.

This review of literature included studies that detailed the use of bone graft substitute in dental situation, animal, *in vivo*, and *in vitro* studies. We excluded studies in the ortho-

pedic and neurosurgery field and those not published in English or Korean. The Google Scholar, ISI Web of Knowledge, PubMed, EMBASE (1980-2019) and Cochrane Databases were searched in February 2019 using the criteria of registered or trademarked product name. The authors read the full text of the studies and classified it according to the ‘level of evidence’ presented by Wright et al.⁹ (Table 1)

Human study level I evidence is a prospective, randomized, or splint-mouth study with definite results that support the use of alloplastic bone substitute in clinical condition. The case report was classified as level IV. Clinical studies used alloplastic bone substitute as carrier of osteoinductive growth factors or as comparison of membrane efficacy have not been evaluated for osteoconductive capacity, but have been assigned to human study level IV as showing clinical stability. The animal, *in vivo*, and *in vivo* study were separately indicated. All authors reviewed each paper and independently assigned evidence levels. If there is a disagreement on the assigned level, discussion and resolution were made. All studied with human study level I, II, III, or IV were included to be citation¹⁰.

III. Results

In December 2018, thirty-seven dental alloplastic substi-

Table 1. Level of evidence for research questions⁹

Type	Level	Description
Published human studies	I	Randomized controlled trial (RCT)
	II	Split-mouth study
		Prospective cohort ¹
	III	Systematic review with level II studies
Poor-quality RCT (e.g., <80% follow-up)		
IV	Case-control study ²	
	Retrospective cohort study ³	
		Systematic review with under level III studies
		Case series or case report no/or historical, control group and poor designed human studies
		Animal studies
		<i>In vivo</i> studies (cell culture)
		<i>In vitro</i> studies

¹Patients were compared with a control group of patients treated at the same time and same institution.

²Patients with a particular outcome (‘cases’) were compared with those who did not have the outcome (‘controls’).

³The study was initiated after treatment was performed.

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tutes were registered in MOHW and HIRA⁸. However, there were two products (BIO-C [Cowellmedi, Busan, Korea] and OssPol-Dental [Genewel, Seongnam, Korea]) that were not commercially available and one product of DualPor COLLAGEN D-INJECTION (OssGen, Daegu, Korea) that was discontinued in the market. Of the remaining 34 alloplastic substitutes, 28 products (82.4%) could be obtained information and included in this review. To approve certificate of GMP from MOHW and MFDS, the company should submit the researches for safety and efficacy of its product, as same procedure as U.S. FDA.(Table 2) The researches, however, were not published and the authors could not include in this review. The available information regarding the delivery form, component, indications, morphology (porosity, biomechanical structure, particle size), and property are shown in Tables 3 to 8.

1. The products approved in FDA

Seven products were approved in FDA¹¹⁻¹⁷.(Table 2) Although TCP Dental (Kasios SAS, L'Union, France) was not licensed for dental indication in intended use of FDA¹⁷. However, the authors included TCP Dental in this category because manufacturer did not distinguish between KASIOS TCP and (KASIOS) TCP Dental.

2. Registered in MOHW and commercially available information for product name, manufacturer, importer, and component

The details of dental alloplastic bone substitute which was approved by MOHW notification No. 2018-248 were analyzed⁸.(Table 3) Among them, BIO-C and OssPol-dental were officially discontinued. CollaOss (SK Bioland, Cheonan,

Table 2. Dental bone graft substitutes which Food and Drug Administration (FDA) 510(k) approved

Product name	Approved date (mo/day/yr)	Indications with FDA 510(k) approved
Cerasorb M granules	7/22/2005	Alveolar augmentation Filling of defects after root resection, apicoectomy, and cystectomy Filling of extraction sockets Elevation of the maxillary sinus floor
MBCP	12/11/2003	Filling of periodontal/perio-implant defects for GTR and GBR Bone void filler for bony voids or gaps of the skeletal system Used with autograft as a bone graft extender Osseous defects and/or from traumatic injury to the bone. Without initial mechanical properties. Therefore, rigid fixation techniques may often be recommended. Gradually resorbs and is replaced with bone.
MBCP Plus, MBCP+	7/30/2007	Periodontal/infrabony defects Ridge augmentation Extraction site (for implant)
OSTEON	7/8/2010	Sinus graft and cyst defect Periodontal/infrabony defects Ridge augmentation Extraction site (for implant) Sinus lifts
OSTEON II	12/26/2011	Cystic cavities Periodontal/infrabony defects Ridge augmentation Extraction site (implant preparation/placement) Sinus lifts
OSTEON III	9/14/2016	Cystic cavities Periodontal/infrabony defects Ridge augmentation Extraction site (implant preparation/placement) Sinus lifts
TCP Dental	11/10/2004	Cystic cavities Cystic cavities Packed into bony voids or gaps of the skeletal system (such as the extremities, spine and the pelvis). Osseous defects and/or from traumatic injury to the bone. Resorbs and is replaced with bone during the healing process. -Approved for KASIOS TCP not (KASIOS) TCP Dental

(GTR: guided tissue regeneration, GBR: guided bone regeneration)

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Table 3. Dental bone graft substitutes with manufactures, importer, components and inconsistency with registered in Korean Ministry of Health and Welfare and Korean Health Insurance Review and Assessment Service

Product name	Manufacturer	Nationality	Importer name	Registered components	Remarks
OSSABASE-HA	LASAK	Czech	Mono Dent	HA	OSSABASE-HA → OssaBase-HA
OVIS BONE HA	DENTIS	Korea	DENTIS	HA	OVIS BONE HA → Ovis BONE HA
COLLAOSS (BLOCK), OOSBONE COLLAGEN	SK Bioland	Korea	SK Bioland	HA (90%±5%)+ collagen (10%±5%)	COLLAOSS (BLOCK), OSSBONE COLLAGEN → CollaOss (BLOCK), OssBone collagen Role out xenograft
COLLAOSS (PUTTY)	SK Bioland	Korea	SK Bioland	HA (90%±5%)+ collagen (10%±5%)	COLLAOSS (PUTTY) → CollaOss (PUTTY) Role out xenograft
COLLAOSS (SYRINGE)	SK Bioland	Korea	SK Bioland	HA (90%±5%)+ collagen (10%±5%)	COLLAOSS (SYRINGE) → CollaOss (SYRINGE) Only block and putty type of CollaOss
DUALPOR COLLAGEN D-PUTTY	OssGen	Korea	OssGen	HA (60%)+bovine atelo collagen (0.3%)+ distilled water (39.7%)	DUALPOR COLLA- GEN D-PUTTY → DualPor Collagen D-Putty HA (60%)+β-TCP (40%)+bovine collagen
DUALPOR COLLAGEN D-INJECTION	OssGen	Korea	OssGen	HA (60%)+bovine atelo collagen (0.3%)+ distilled water (39.7%)	DUALPOR COLLAGEN D-INJECTION → DualPor Collagen Injection NA
BONESIGMA TCP	SigmaGraft	USA	KodentTMS	β-TCP 100%	BONESIGMA TCP → BoneSigma TCP
EXCELOS INJECT	BioAlpha	Korea	BioAlpha	β-TCP etc.	EXCELOS INJECT → Excelos INJECT BioAlpha → CGbio
EXCELOS (TCPGLD)	BioAlpha	Korea	BioAlpha	β-TCP 100%	EXCELOS (TCPGLD) → Excelos (TCPGLD) BioAlpha → CGbio
EXCELOS (TCPGMD, TCPGLD)	BioAlpha	Korea	BioAlpha	β-TCP 100%	EXCELOS (TCPGMD, TCPGLD) → Excelos (TCPGMD, TCPGLD) BioAlpha → CGbio
MEGA-TCP (CGL)	CGbio	Korea	CGbio	β-TCP 100%	MEGA-TCP (CGL) → Mega-TCP CG bio → MegaGen
Mega-TCP (CGM, CGL)	CGbio	Korea	CGbio	β-TCP 100%	MEGA-TCP (CGM, CGL) → Mega-TCP NA
SORBONE	META-BIOMED	Korea	META-BIOMED	β-TCP 100%	SORBONE → Sorbone
SYNCERA	Oscotec	Korea	Oscotec	β-TCP	SYNCERA → Syncera
CERASORB	Curasan	Germany	B.ITRADING	β-TCP	Cerasorb → Cerasorb M
BIO-C	Cowellmedi	Korea	Cowellmedi	β-TCP+HA	NA
BONCELOS	BioAlpha	Korea	BioAlpha	β-TCP+HA	BONCELOS → Boncel-Os BioAlpha → CGbio
BONESIGMA BCP	SigmaGraft	USA	KODENT TMS	β-TCP (40%)+HA (60%)	BONESIGMA BCP → BoneSigma BCP
CERASORB M GRANULES	Curasan	Germany	Mono Dent	β-TCP+HA	CERASORB M GRANULES → Cerasorb M HA+β-TCP → 99% β-TCP

Table 3. Continued

Product name	Manufacturer	Nationality	Importer name	Registered components	Remarks
FRABONE DENTAL	Inobone	Korea	Inobone	β -TCP (40% \pm 5%)+ HA (60% \pm 5%)	FRABONE DENTAL → FRABONE
FRABONE DENTAL INJECT	Inobone	Korea	Inobone	β -TCP+HA	FRABONE DENTAL INJECT → FRABONE-Inject Hyaluronic acid addition
GENESIS-BCP	DIO	Korea	DIO	β -TCP (40%)+HA (60%)	N/S
MBCP	Biometlante	France	Purgo Biologics	β -TCP+HA	N/S
MBCP PLUS	Biometlante	France	Purgo Biologics	β -TCP+HA	MBCP PLUS → MBCP or/with syringe type
NEW BONE	GENOSS	Korea	GENOSS	β -TCP+HA	NEW BONE → Newbone
OSSPOL DENTAL	Genewel	Korea	Genewel	β -TCP (40%)+HA (60%)	OSSPOL DENTAL → OssPol
OSTEON	GENOSS	Korea	GENOSS	HA (β -TCP)	NA
OSTEON II	GENOSS	Korea	GENOSS	β -TCP+HA	N/S
OSTEON III	GENOSS	Korea	GENOSS	β -TCP+HA	N/S
OSTEON III COLLAGEN	GENOSS	Korea	GENOSS	β -TCP+porcine collagen (95%)	N/S
OSTEON SINUS	GENOSS	Korea	GENOSS	HA (β -TCP)	Only syringe type of OSTEON I, II, and III
OVIS BONE HA	DENTIS	Korea	DENTIS	β -TCP+HA	OVIS BONE HA → Ovis BONE HA
TCP Dental	Kasios SAS	France	B.IMTECH	β -TCP (95%)+HA (5%)	β -TCP (95%)+HA (5%) → β -TCP (99.9%)
Q-OSS+	OSSTEM IMPLANT	Korea	OSSTEM IMPLANT	β -TCP (80% \pm 5%)+ HA (20% \pm 5%)	N/S
TOPGEN-S	Toplan	Korea	Toplan	β -TCP (80% \pm 5%)+ HA (20% \pm 5%)	N/S
INNO CAP	Cowellmedi	Korea	Cowellmedi	Calcium phosphate (100%)	INNO CAP → INNO-CaP

(HA: hydroxyapatite, β -TCP: β -tricalcium phosphate, NA: not available, N/S: nothing special)

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Korea) is registered as 60% of HA, 0.3% of bovine-derived collagen (0.3%) and 39.7% of distilled water and as block, syringe and putty types. Currently, only block and putty type are available in the manufacturer. DualPor COLLAGEN D-PUTTY and DualPor COLLAGEN D-INJECTION is available as DualPor Collagen D-Putty and DualPor Collagen Injection, but no any information could be found.

There are seven products that do not match the manufacturer or importer registered in MOHW: (1) MBCP+ (Biometlante, Vigneux-de-Bretagne, France; sold only as MBCP and MBCP syringe type, not MBCP+), (2) Excelos Inject (BioAlpha, Seongnam, Korea; produced by CGbio, Seongnam, Korea), (3) Excelos (TCPGLD) (BioAlpha; produced by CGbio, sold exclusively by Excelos), (4) Boncel-Os (BioAlpha; produced by CGbio), (5) Mega-TCP (manufactured by CGbio; MegaGen, Seoul, Korea, sold as a single product without discrimination between CGM and CGL), (6) Cerasorb and Cerasorb M granule (sold only by Curasan, Kleinostheim, Germany: Cerasorb M, registered as importer) BI Trading

currently available is not available), and (7) OSTEON Sinus (GENOSS, Suwon, Korea: sold as syringe type of OSTEON I, II, or III).(Table 3)

CollaOss is listed as a dental synthetic bone in the MOHW and HIRA data. Although it was represented as xenograft in the journal¹⁸⁻²¹; however, it was included in this review.(Table 3)

There are three products that do not match in the component registered in MOHW: (1) Cerasorb M granules (99% β -TCP not β -TCP combined with HA; Curasan), (2) FRABONE-Inject (Inobone, Cheonan, Korea: hyaluronic acid addition with HA+ β -TCP), and (3) TCP Dental (99% β -TCP not 95% β -TCP combined with 5% HA).(Table 3)

As a result, out of the 33 dental bone substitutes that are currently registered in MOHW and HIRA, 28 products could be commercially available when considering the products that are different form registered information as below: Excelos (TCPGLD) and Excelos (TCPGMD, TCPGLD) are sold exclusively by Excelos, Mega-TCP (CGL) and Mega-

TCP (CGM, CGL) are sold only by Mega-TCP, Cerasorb and Cerasorb M granules are sold by Cerasorb M, Cerasorb M is 99% β -TCP, FRABONE-Inject is sold by adding hyaluronic acid, CollaOss is sold in putty and block form without syringe type, DualPor COLLAGEN D-INJECTION is not produced, and TCP Dental (99% β -TCP).

3. Analysis of dental alloplastic bone substitutes according to constituents

The main components of dental alloplastic bone substitute are tricalcium phosphate ($\text{Ca}_3(\text{PO}_4)_2$, β -TCP), calcium phosphate (CaP), and hydroxiapatite ($\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$, HA) which is crystalline form of CaP.(Table 4)

1) Dental alloplastic bone substitutes consist of hydroxyapatite

HA is an inorganic material which account for 65% of bone matrix and can be classified as dense and porous, sintered ceramic and non-ceramic, and bovine, coralline and synthetic depending on the origin. Typical characteristics are as below. (1) As large as the particle size, it remains for a long time with slow absorption. (2) The higher the porosity, the easier the penetration of new bone and the quicker absorbed. (3) The larger the crystallinity, the longer the absorption period. (4) Rigid and dense block-form products have high compressive strength but are susceptible to fracture. (5) The higher the porosity, the lower the strength⁵.

Among the dental alloplastic bone substitutes allowed for use in Korea, there were four products that consisted of HA. OssaBase-HA (LASAK, Praha, Czech) has a retrospective study of guided bone regeneration in 2018, but it was obtained human study level IV due to a poor study design²². However, many other animal, *in vivo*, and *in vitro* studies for osteoconductivity²³⁻²⁶. No journals were found for Ovis BONE HA (DENTIS, Seoul, Korea). CollaOss consists of 90% porcine-derived HA and 10% porcine derived collagen. It was classified as alloplastic graft in MOHW and HIRA, on the other hands, it was introduced as xenograft in many studies¹⁸⁻²¹. In the manufacturer (SK Bioland), it is commercially available in plug type and putty type. In comparison with the collagenated bovine bone (Bio-Oss collagen; Geistlich Biomaterials, Woulhusen, Switzerland) into the extraction socket, it was received the human study level III because there was no difference in the efficacy¹⁸. Human study level IV was received in a clinical study to compare the effects of membranes on peri-implant defect¹⁹. Animal studies showed

Table 4. Commercially available dental alloplastic bone substitutes according to components

Commercially available dental alloplastic bone substitutes	Total (n=28)
Hydroxyapatite (HA)	4
β -Tricalcium phosphate (β -TCP)	8
β -TCP+HA	15
Calcium phosphate (CaP: composition not confirmed)	1

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osteoconductivity^{20,21}.(Table 4)

2) Dental alloplastic bone substitutes consist of tricalcium phosphate

TCP has a composition of calcium and phosphorus in ratio of 3 and 2. It was known as partially transition into HA and absorption *in vivo*, but various absorption periods of three to 24 months have been reported depending on the products. The rate of absorption varies according to the chemical structure, porosity and particle size of the material⁵. The general characteristics suggested by the manufacturer of TCP are as follows. (1) Use with platelet-rich plasma is effective. (2) It is absorbed at the same time as new bone graft. (3) Due to the interconnection of the pores, bone fibers are rapidly penetrated and could promote the regeneration. (4) Since the particle is rounded, there is little mechanical irrigation in surrounding tissues and little inflammatory reaction. (5) High mechanical stability prevents early collapse and inhibits undesirable macrophage activity.

Of the approved products for Korean dental alloplastic bone substitute, seven products that consist with TCP were commercialization. BoneSigma TCP (SigmaGraft, Fullerton, CA, USA) has been described as one of the *in vitro* studies²⁷, and clinically available products^{28,29} but no clinical studies have been published. Excelos is registered as β -TCP etc. in MOHW and has two types of powder and injection and registered. Injection type is a mixture of biodegradable polymers such as poloxamer and hydroxypropyl methylcellulose (HPMC) to enhance injectable property, moldability and hemostasis. A clinical study comparing putty type Excelos with extraction and using as BMP carriers received a human study level IV³⁰. Excelos has animal studies for BMP carrier^{31,32} and *in vivo* study for osteoconduction³³. No journals were found for Mega-TCP. Sorbone (META-BIOMED, Cheongju, Korea) was validated and received human study level II by a split-mouth study as a control of cockle-shell bone substitute in socket preservation³⁴, and used as a control material for the effect of alendronate on periodontal intra-osseous defect³⁵.

SynCera (Oscotec, Seongnam, Korea) had animal and *in vivo* study for osteoconductivity^{36,37}. Cerasorb was approved by the FDA and commercially available to Cerasorb M which reduced porosity from 80% to 65%¹¹. It was received human study level I by randomized controlled trial and systematic review that was equivalent to an autogenous graft in sinus lift^{38,39}. It was received human study level III in cystic lesion, periodontal defect and cleft alveolus⁴⁰. Also, as a result of histologically sufficient alveolar bone regeneration, human study level III was obtained in extraction socket⁴¹. As human study level IV, it was used with an enamel matrix derivative in the periodontal defect^{42,43}, peri-implant defect after immediately implantation after extraction⁴⁴, every lots of animal, *in vivo*, and *in vitro* studies for osteoconduction^{6,45-56}. TCP Dental was registered as 5% of HA and 95% of β -TCP in MOHW and HIRA. However, the manufacturer (Kasios SAS) and importer (B.IMTECH, Yongin, Korea) advertised as 99% of β -TCP. Many studies and FDA 510(k) also represented as β -TCP^{17,57-65}. It was received human study level III by successful histologic and clinical result comparing Xenograft (BonePlus-xs; Integros, Adana, Turkey) in sinus lift⁵⁷. Ani-

mal, *in vivo*, and *in vitro* studies for osteoconductivity⁵⁸⁻⁶⁵.

3) Dental alloplastic bone substitutes consist with hydroxyapatite and tricalcium phosphate

The mixing ratio of HA and TCP varies from 2:8 to 7:3. It has the following characteristics. (1) It has micropore and macropore. They could induce effective tissue reaction and growth of new bone tissue. Micropores could enable ion exchange and form new contact surfaces for cell adhesion through the deposition of bone crystals. Macropores could help in angiogenesis and remodeling and growth of new bone. (2) HA acts as a mechanical support until the new bone tissue could be remolded for structural stability, and TCP could spread the adhesion surface of osteoblast by ion exchange through rapid resorption. (3) It has porosity of 70% to 90%⁵.

Boncel-Os (CGbio) consists with 30% of HA and 70% of β -TCP. It was introduced as one of the clinically available products⁶⁶, and there is an animal study used as a BMP carrier⁵⁶. BoneSigma BCP (SigmaGraft) consists with 60% of HA and 40% of β -TCP. *In vivo* study has been published that

Table 5. Dental bone graft substitutes which was consisted with hydroxyapatite (HA)

Product name	Delivery	Component	Indication	Morphology	Property	Level of evidence
OssaBase-HA	Granule	HA:CaP (1.65), Ca ₁₀ (PO ₄) ₆ (OH) ₂	Remodeling of the alveolar ridge Treatment of periodontal defects Treatment of bone defects around dental implants Sinus lift Filling of bone defects after surgical extractions to prevent alveolar atrophy Filling of bone defects after extirpation of cysts	Macro-nano bone like structure 83% interconnected porosity Narrow size ranges of available granules Enough space for bone ingrowth over large distances	Volume maintenance Low substitution rate No risk of immunological reactions or pathogen transmission	Human study level (IV: GBR ²²) Animal, <i>in vivo</i> , <i>in vitro</i> studies
Ovis BONE HA	Granule	100% HA	Periodontal bone defect Intrabony defect Extraction site Ridge augmentation Sinus lift Cystic cavity	Well-formed macro/micro porous Porosity	Osteoconductivity Biocompatibility Non toxicity Non inflammatory nature Easy manipulation	NA
CollaOss (Block), Ossbone Collagen	Plug	HA 90%±5%+ collagen 10%±5%	Periodontal bone defect Intrabony defect	Well-formed macro/micro porous Porosity	Easy manipulation and adhesion due to collagen Slow absorption and partial remodeling	Human study (III: extraction socket ¹⁸ , IV: peri-implant defect ¹⁹)
CollaOss (Putty)	Granule	HA 90%±5%+ collagen 10%±5%	Periodontal bone defect Intrabony defect	Well-formed macro/micro porous Porosity	Easy manipulation and adhesion due to collagen Slow absorption and partial remodeling	Animal study

(CaP: calcium phosphate, GBR: guided bone regeneration, NA: data not available)

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Table 6. Dental bone graft substitutes which was consisted with β -tricalcium phosphate (β -TCP)

Product name	Delivery	Component	Indication	Morphology	Property	Level of evidence
BoneSigma TCP	Powder	β -TCP 100%	Extraction socket Horizontal and vertical augmentation Peri-implant defects Periodontal regeneration Ridge augmentation Sinus floor elevation Sinus lift Guided bone regeneration Socket preservation	>95% β -TCP Interconnected macro and micro porous structure	Osteoconductive High resorption rate: rapid osseointegration and recovery in dental implants	<i>In vitro</i> study
Excelos Inject	Injectable	β -TCP 100%	Sinus floor elevation Sinus lift Guided bone regeneration Socket preservation	β -TCP particle (size: 45-75 μ m) with hydrogel (poloxamer, hydroxypropyl methylcellulose [HPMCC])	Hemostasis and injectable by poloxamer-based hydrogel High moldability Osteoconductive High resorption rate Space maintaining for new bone formation	Human study level (IV: extraction socket ³⁰) Animal studies (for BMP carrier), <i>in vivo</i> , <i>in vitro</i> studies
Excelos (TCPGLD)	Powder	β -TCP 100%	Sinus floor elevation Alveolar bone augmentation Extraction socket preservation	100% β -TCP Average 80% macro-porosity (pore size: 100-300 μ m)	Osteoconductive Faster absorption and biodegrade rate Space maintaining for new bone formation	Animal, <i>in vitro</i> studies
MEGA-TCP (CGL)	Powder	β -TCP 100%	NA	Porous structure like human cancellous bone >99% interconnectivity Average 75% macro-porosity (pore size: 100-300 μ m) Average 55%-60% macro-porosity	Biocompatibility Biodegradable	NA
Sorbone	Powder	β -TCP 100%	Extraction socket Cystic cavities Periodontal defects Intrabony defects Ridge augmentation Sinus floor elevation	Macro- and micro-porosity	Osteoconductive High resorption rate Biocompatibility Easy handling	Human study (level II, socket preservation ³⁴ and periodontal defect ³⁵)
SynCera	Powder	β -TCP 100%	NA	Macro- and micro-porosity	Osteoinduction >70% new bone formation 99% resorption	Animal, <i>in vivo</i> , <i>in vitro</i> studies
Cerasorb M	Powder	β -TCP 99%	Augmentation or reconstructive treatment of alveolar ridge Infrabony periodontal defects Defects after root resection, apicoectomy, and cystectomy Extraction socket Sinus lift Guided tissue regeneration Guided bone regeneration Peri-implant defect	Micro-meso-macro pore (pore size 5-500 μ m) about 65% porosity with full range of pore size and interconnected porosity	Optimal microenvironment for osteoblast adhesion proliferation and Subsequent bone remodeling	Human study level (I: sinus ^{38,39} , III: cystic lesion, periodontal defect, cleft alveolus ⁴⁰ , extraction socket preservation ⁴¹ , IV: peri-implant defect ^{42,43}) Animal, <i>in vivo</i> , <i>in vitro</i> studies
TCP Dental	Granule	β -TCP 99%	Sinus graft Bone loss correction Filling alveoli Periodontology	Interconnected macro-porosity >90% porosity (pore size: 0.2-0.5 mm) Particle size: 0.15-2.0 mm	Osteoconductive Early resorbable and angiogenesis	Human study (III: sinus graft ⁵⁷) Animal, <i>in vivo</i> , <i>in vitro</i> for osteoconduction

(BMP: bone morphogenetic proteins, NA: data not available)

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Table 7. Dental bone graft substitutes which was composed with hydroxyapatite (HA) and β -tricalcium phosphate (β -TCP)

Product name	Delivery	Component	Indication	Morphology	Property	Level of evidence
Boncel-Os	Granule	β -TCP (70%)+ HA (30%)	Ridge augmentation Extraction sockets Periodontal defect Sinus lift	High porosity Interconnected porous structure	High biocompatibility Osteoconduction Excellent wettability	Animal study
BoneSigma BCP	Granule	β -TCP (40%)+ HA (60%)	Ridge augmentation Extraction sockets Cystic cavities Sinus floor elevation Periodontal defects Peri-implant defects NA	Micro- and macro-porosity	Osteoconductive properties Long-term volume stability	<i>In vivo</i> study
DualPor COLLAGEN D-PUTTY	Block	β -TCP (40%)+ HA (60%)+ bovine collagen (5.5%)	NA	Trabecular like structure Interconnected macro- and micro-porosity 80% of porosity	Biocompatibility Bioabsorbable Easy handling and moldable Hemostasis and anti-adhesion effect Biocompatibility Bioactive	NA
FRABONE	Granule	β -TCP (40%)+ HA (60%)	NA	Haversian canal like structure (international patent: PCT/ KR2011/005509-USA and Germany), 150-300 μ m macropore Average 8.1 μ m micropore 0.7 mm size of porous particles	Osteoconductivity Osteoinductivity Mechanical strength Structural feature reserves stable room and filled up with vessels and new bone material, resulting in faster regeneration	NA
FRABONE -Inject	Injection	β -TCP (40%±5%)+ HA (60%±5%)+ coated with hyaluronic acid	NA	Haversian canal like structure (international patent: PCT/ KR2011/005509-USA and Germany), 100-300 μ m micropore 0.7 mm size of porous particles	Highly biocompatible and bioresorbable due to hyaluronic acid Osteoconductivity High mechanical strength Structural feature Moldability	NA
GENESIS-BCP	Granule	β -TCP (40%)+ HA (60%)	NA	70% of complete interconnected porosity 75% macropore (300-700 μ m) 25% micropore (<10 μ m)	Injectability High mechanical strength Highly biocompatible	Human studies (level II: periodontal defect ⁷⁰ , level IV: horizontal augmentation ⁷¹) Animal, <i>in vivo</i> , <i>in vitro</i> studies for osteoconduction Human study (level IV: extraction socket ⁶⁴) Animal, <i>in vivo</i> , <i>in vitro</i> for osteoconduction
MBCP Plus	Granule	β -TCP (80%)+ HA (20%)	Sinus lift augmentation Ridge augmentation Alveolar regeneration Alveolar regeneration Intra-osseous pockets	70% porosity with 35% microporosity 1/3 micropores (<10 μ m) 2/3 macropores (300-600 μ m)	Permeable Resorbable Hydrophilic Bioactive Osteoconductive Regeneration	

Table 7. Continued

Product name	Delivery	Component	Indication	Morphology	Property	Level of evidence
NEW BONE	Granule	β-TCP (80%)+ HA (20%)	Ridge augmentation Extraction site and osteotomy Cystic cavities Sinus lift	80% porosity (pore size: 200-400 μm) 0.2-2.0 mm size of porous particles	Osteoconductive synthetic bone graft Highly resorbable due to 80% β-TCP Easy manipulation	Animal study
OSTEON	Granule/ syringe	β-TCP (30%)+ HA (70%)	Periodontal defect Periodontal/infrabony defects Ridge augmentation Extraction site (implant preparation/placement) Sinus lift Cystic cavities	HA coated with β-TCP Interconnected porous structure similar to that of human cancellous bone 77% porosity (pore size: 300-500 μm) Irregular shaped particles of size Particle size (granule): 0.3-2.0 mm Particle size (sinus, syringe): 0.5-2.0 mm Particle size (lifting, syringe): 0.3-1.0 mm	Osteoconductive	Human study (level III: sinus lift ⁹⁴) Animal, <i>in vivo</i> , <i>in vitro</i> for osteococonduction
OSTEON II	Granule/ syringe	β-TCP (70%)+ HA (30%)	Periodontal/infrabony defects Ridge augmentation Extraction site (implant preparation/placement) Sinus lift Cystic cavities	Interconnected porous structure similar to that of human cancellous bone >70% porosity (pore size: 250 μm) Irregular shaped particles of size Particle size (granule): 0.2-2.0 mm Particle size (sinus, syringe): 0.5-2.0 mm Particle size (lifting, syringe): 0.2-1.0 mm	Highly resorbable due to higher β-TCP content Easy manipulation Excellent wettability Osteoconductive	Human study (level III: extraction socket ⁹⁹ , level IV: sinus lift ¹⁰⁰ , vertical ridge augmentation ¹⁰¹ , ridge augmentation ^{102,103} , periodontal defect ¹⁰⁵) Animal, <i>in vivo</i> for osteococonduction
OSTEON III	Granule/ syringe	β-TCP (40%)+ HA (60%)	Periodontal/infrabony defects Ridge augmentation Extraction site (implant preparation/placement) Sinus lift Cystic cavities	Interconnected macro and micro porous structure <80% porosity Particle size (granule): 0.2-2.0 mm Particle size (sinus, syringe): 0.5-2.0 mm Particle size (lifting, syringe): 0.2-1.0 mm >70% crystallinity CaP=1.59 Particle size: 0.2-1.0 mm	Biocompatible Osteoconductive	Animal study (BMP carries)
OSTEON III Collagen	Cylinder	β-TCP (40%)+ HA (60%)+ type I collagen (>95% porcine tendon collagen)	Alveolar bone defect		Easy manipulation Excellent wettability	NA
Ovis BONE BCP	Granule	β-TCP (80%)+ HA (20%)	Periodontal bone defect Infrabony defect Extraction site Ridge augmentation Sinus lift Cystic cavity	70% porosity (pore size: 20 μm) Particle size: 0.3-2.0 mm	Osteoconductive Excellent wettability Easy manipulation Biocompatibility and great bioactivity	NA

Table 7. Continued

Product name	Delivery	Component	Indication	Morphology	Property	Level of evidence
Q-OSS+	Granule	β -TCP (80%)+ HA (20%)	NA	Porous structure	Excellent hydrophilicity Osteoconductive Biocompatible Bioabsorbable	Cell culture
TOPGEN-S	Granule	β -TCP (80%)+ HA (20%)	NA	Interconnected macro and microporous Particle size: 1.0-2.0 mm	Rapid osteogenesis rate Excellent hydrophilicity Osteoconductive	NA

(NA: data not available, CaP: calcium phosphate, BMP: bone morphogenetic proteins)
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it inhibited osteoclast formation with plate-rich fibrin⁶⁷. Dual-pore Collagen D-Putty was registered as 60% of HA, 0.3% of bovine-derived collagen, and 39.7% of distilled water by the MOHW and HIRA. On the other hand, the manufacturer (Os-sGen) advertised the product as 60% HA and 40% β -TCP in 94.5% of biphasic CaP, and with an additional 5.5% bovine collagen but there are no reports of any evaluations of the evaluating its information provided. In MOHW and MFDS, Inobone has registered its products as FRABONE DENTAL and FRABONE DENTLA INJECT, but they are commercially available as FRABONE and FRABONE-Inject. FRABONE (Inobone) consists with 60% of HA and 40% of β -TCP and it was received patent in USA, Germany, and Korea as mimic the harversian canal structure^{68,69}. FRABONE-Inject (Inobone) is a product of hyaluronic acid addition to FRABONE, which advertised to increase moldability and absorption rate by act as soluble granules of hyaluronic acid. However, there was no related researched were found. GENESIS-BCP (DIO, Busan, Korea) consists with 60% of HA and 40% of β -TCP. It was received human study level II by prospective controlled clinical trial which results good outcome in periodontal defect⁷⁰. In horizontal augmentation, it was showed successful result with NanoBone (HA and silica gel matrix; Artoss GmbH, Warnemünde, Germany) in case report and it obtained human study level IV⁷¹. There were many animal, *in vivo*, and *in vitro* studies for osteoconductivity⁷²⁻⁷⁷. Manufacturers have the two types of MBCP as combination of HA and β -TCP as ratio as 60:40 and 20:80, and a moldable MBCP (In'Oss) made by mixing hydrogel to MBCP. However, represented importer (Purgo Biologics, Seongnam, Korea) only has granule or syringe type of MBCP+ which consists with 20% of HA and 80% of β -TCP. MBCP and MBCP+ were received in FDA 510(k) approved^{12,16}. There were many clinical studies from MBCP which consists with 60% of HA and 40% of β -TCP⁷⁸⁻⁸⁴. On the other hand, MBCP+ was published only animal studies⁸⁵⁻⁸⁸ and *in vitro* studies^{89,90}. Although not introduced as MBCP+, a combination of 20% of HA and 80% of β -TCP was as same resorption and bone growth as combination of 60% of HA and 40% of β -TCP in retrospective clinical trial for extraction socket and it could be human study level IV⁸⁴. Newbone (GENOSS) consists with 20% of HA and 80% of β -TCP. Although there were animal and *in vivo* studies for osteoinductivity⁹¹⁻⁹³, no clinical studies were found. Boncel-Os consists with 30% of HA and 70% of β -TCP. It was introduced as one of clinically available products⁶⁶ and used as BMP carrier in animal study⁵⁶.

OSTEON series (GENOSS) were available as vial, sinus,

Table 8. Dental bone graft substitutes which was consisted with calcium phosphate

Product name	Delivery	Component	Indication	Morphology	Property	Level of evidence
INNO-CaP	Granule	Calcium phosphate (100%)	Sinus lift Guided bone regeneration	0.41-1.4 mm of particle size	Completely resorpted and progressively replaced by normal-structured bone Biocompatibility Osteoconductivity Safety	NA

(NA: data not available)

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and lift type. OSTEON, OSTEON II, and OSTEON III were received FDA 510(k) approval¹³⁻¹⁵. In registration of MOHW and HIRAO, OSTEON and OSTEON Sinus were separated but OSTEON Sinus is not available product to commercially use. The manufacture (GENOSS) has classified OSTEON Sinus and OSTEON Lifting according to the size of syringe. In FDA 510(k), there also received approval as same as OSTEON, OSTEON Sinus, and OSTEON Lifting¹³. OSTEON consists with 70% of HA and 30% of β -TCP. In retrospective clinical study for sinus lift, OSTEON alone could result well-developed lamellar bone as same as Xenograft (Bio-Oss; Osteohealth, Shirley, NY, USA) and it could be received human study level III⁹⁴. There were many animal and *in vivo* studies for osteoconductivity⁹⁵⁻⁹⁸. OSTEON II consists with 30% of HA and 70% of β -TCP. In retrospective clinical study for extraction socket, OSTEON II and OSTEON II Collagen were significantly more effective than collagen or native defect and the histological result was shown in animal studies⁹⁹. Therefore, it could be received human study level III in extraction socket. It was received human study level IV by retrospective study as control group for sinus lift¹⁰⁰, 6 months after vertical augmentation which particulated OSTEON II was showed no significantly difference on volume change and peri-implant marginal bone loss compared with autogenous block and allogeneous block bone¹⁰¹, successful results on clinical and histologically in ridge augmentation^{102,103}, successful outcome on graft after implant removal¹⁰⁴, and clinically effective on periodontal defect¹⁰⁵. Many animal and *in vivo* studies for osteoconductivity^{95-97,106,107}. OSTEON III consists with 60% of HA and 40% of β -TCP. There was animal study as BMP carrier¹⁰⁸. Although there was no OSTEON III Collagen related study, OSTEON II Collagen had animal and *in vivo* studies for osteoconductivity^{109,110}. Ovis BONE BCP (DENTIS) consists with 20% of HA and 80% of β -TCP. No journals were found for Ovis BONE BCP. Q-Oss+ (OSSTEM IMPLANT, Seoul, Korea) consists with 20% of HA and 80% of β -TCP. It was received human study level IV by the clinical study on

peri-implant defect¹¹¹. There were *in vivo* study for osteoconductivity¹¹² TOPGEN-S (Toplan, Seoul, Korea) consists 20% of HA and 80% of β -TCP and there could not be found for journals for TOPGEN-S.

4) Dental alloplastic bone substitutes consist with CaP (composition not confirmed)

INNO-CaP (Cowellmedi) was advertised that consists CaP, however, the composition was not clearly known and no relevant research were found.

IV. Discussion

Commercially available dental alloplastic bone substitute which was approved MOHW notification No. 2018-248 were broadly divided into 4 groups as C group (bone union and fixation group), L group (general materials), T group (human tissue), and non-insurance group. In the subcategory, there were C0 group (bone substitutes: xenograft, alloplastic graft), L7 group (dental material: dental xenograft, dental alloplastic graft), TB group (bone, demineralized bone matrix, bone block, bone chip, bone powder), non-insurance group (treatment material, human-derived bone, bone substitute containing bone morphogenetic protein [rhBMP-2])⁸. Among them, dental alloplastic bone substitutes in L7 of L group were included in this study.

The post-application management is obligatory for the manufacturer (or representative importer) to receive a certification of GMP by MFDS. According to FKDS No. 2016-156 of 'medical device manufacturing and quality control standards', the certification of GMP of human tissue or functional replacement product should be renewed every three years in article 9. According to article 10 of KFDS No. 2016-156, the certification of GMP should be reissued when any information for the products changed (change of the name of the importer or manufacturer, change of location of the importer or manufacturer). In article 12 and 15, the quality

control examination agency reports periodic on the compatibility of medical device to director of KFDA⁷. Therefore, the manufacturer or importer of registered in the MFDS could be important factors in terms of quality control of currently available bone substitutes.

However, nineteen products (51.4%) were different information among the 37 products registered in MOHW. Four products (10.8%) were different registered ingredients from journal or advertisement including DualPor COLLAGEN D-PUTTY (OssGen), Cerasorb M granules, FRABONE-Inject, and TCP Dental. Nine products (24.3%) were differ in product name or not available including CollaOss (Syringe), Mega-TCP (CGL), Cerasorb, Cerasorb M granules, BIO-C, Excelos (TCPGMD, TCPGLD), MBCP Plus (Biometlante), OssPol DENTAL, and OSTEON Sinus. Especially, CollaOss (Block) and CollaOss (Putty) were registered as dental alloplastic bone substitute in MOHW but they were introduced as xenograft in advertisement and journals. Five products (13.5%) had different manufacturer or importer including Excelos Inject (CGbio), Excelos (TCPGLD), Excelos (TCPGMD, TCPGLD), Mega-TCP (CGM, CGL), Boncel-Os.

For a successful clinical outcome, it cannot be overemphasized that the quality of the materials or medical device should be constant and strictly controlled. Unfortunately, it is hard to identify the certification of GMP or to verify the quality in every clinical situation. Therefore, it is necessary to leave certificate to the government agency or the company which is responsible for the product. In addition the related dental institute or academy should to consider the security on quality of the product.

Implant dentistry has become a common treatment in Korea, many studies and development have been made on implant and bone graft materials. Among dental alloplastic bone substitutes which were registered in MOHW, twenty-nine (78.4%) products were domestically produced, of which three out of seven approved by FDA were made in Korea¹¹⁻¹⁷. However, there are only ten products (27.0%) have been published with clinical study, of which six are Korean products. In the view of reference, the reference level could not be as directly same as the efficiency of the product, but it could be the basis of product selection for the clinician since minimal safety and efficiency can be regarded as verified. Reference level I received Cerasorb M (β -TCP 99%) as a sinus lift^{38,39}. Reference level II received Sorbone (β -TCP 100%) in extraction socket and periodontal defect^{34,35}, GENESIS-BCP (β -TCP 40% and HA 60%) in periodontal defect⁷⁰. Reference level III received Cerasorb M (β -TCP 99%) in cystic cavity, periodon-

tal defect, cleft defect and extraction socket^{40,41}, CollaOss (HA 90% and collagen 10%) in extraction socket¹⁸, OSTEON (β -TCP 30% and HA 70%) in sinus lift⁹⁴, OSTEON II (β -TCP 70% and HA 30%) in sinus lift⁹⁹, TCP Dental (β -TCP 99.9%) in sinus lift⁵⁷. Reference level IV is insufficient to verify the efficiency, could be seen as a step that clinically confirms safety. Cerasorb M was in peri-implant and periodontal defect⁴²⁻⁴⁴, CollaOss was in peri-implant defect¹⁹, OssaBase-HA (HA 100%) was in guided bone regeneration²², Excelos (β -TCP 100%) was in extraction socket³⁰, MBCP+ (β -TCP 80% and HA 20%) was in extraction socket⁸⁴, GENESIS-BCP was in ridge augmentation⁷¹, OSTEON II was in sinus lift¹⁰⁰, ridge augmentation¹⁰¹⁻¹⁰³, periodontal defect¹⁰⁵ achieved for reference level IV. In addition, there were many animal, *in vivo*, and *in vitro* studies for osteoconductivity or role as carrier of osteoinductive growth factors or control material. In order to obtain MOHW and MFDS approval for commercial use in Korea, a data based on research or experiments should be required, but these data could not be included in this study because they were not publicly available. Because dental bone graft surgery has been performed in various environments such as sinus lift, ridge augmentation, cystic lesion, periodontal defect, peri-implant defect, extraction socket, it could be difficult to obtain high reference level in all dental bone grafting fields. However, it is nevertheless necessary to demonstrate the clinical level of Korean dental operation and the development level of bone graft substitutes.

In conclusion, there is not enough information about the effectiveness and safety of currently available alloplastic bone substitute in dental performance. Further clinical trials including well designed RCTs are necessary to evaluation the clinical efficacy of dental alloplastic bone substitutes in Korea. It should be aware of the limited information and developed the clinical evidences and regulations for clinicians.

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Authors' Contributions

J.K.K. performed study, participated in data collection and wrote the manuscript. I.H. attributed to write the manuscript.

B.K.L. and P.Y.Y. analyzed the study, J.K.L. helped in drafting the manuscript and helped in study design. All authors read and approved the final manuscript.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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